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CHEMISTRY, HEREDITY AND DISEASE*

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Recent advances in biochemistry, genetics and virology have not only increased our knowledge of metabolism in the normal and diseased organism, but have also increased the demands upon the physician to become better acquainted with these 3 basic fields of scientific endeavor. Workers in these disclipines as they delve further into the cellular and subcellular levels of research have discovered an increasing correlation and often an overlapping of their activities, resulting in a more integrated approach to these problems and greater stress on the value of teamwork. The clinician can and should be a valuable member of this team. This review is an attempt to correlate some of the major investigations in these fields.

GENETIC PRINCIPLES AND CONSIDERATIONS. Following the advent of the Mendelian concepts of heredity in the latter part of the last century, attention was almost exclusively focused on cross breeding experiments and statistical interpretation of the data obtained from such experiments. Geneticists concentrated for many decades on observing and evaluating changes in the higher plants such as the garden pea, corn, and maize, and in the animal and insect such as the fruit fly, the mouse and occasionally in man. The gene was defined as the unit of inheritance and it was soon concluded that several hundred of these genes are strung together in a row, linked to each other in some fashion, and these strings are microscopically identifiable as the chromosomes. These chromosomes (there are 23 to 24 pairs in every human cell) are located in the nucleus. The chromosome, therefore, carries the hereditary traits and the gene responsible for a specific trait is thought to be located in a certain position or locus in the fibrils that make up the chromosome.

Hans Ris[59] has reviewed the evidence regarding the basic structure of the chromosome as revealed by electron

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microscopy studies and he presents the following observations:

1. The basic morphological unit of the chromosome is the chromofibril, which is approximately 200 A° thick. He suggests that this fibril is made up of nucleic acids and proteins in specific arrangements and combinations.
2. The number of chromofibrils present in a chromosome varies in different species and it is believed that the exact number of such fibrils per chromosome will be a function of the power of 2. This variation in the number of chromofibrils per chromosome may be one factor in causing the differences in the basic amount of deoxyribose nucleic acid (DNA) per chromsome (and therefore per nucleus) of different species. Mazia[50] and Ambrose[5,6,7] suggest that the chromofibril is composed of an end to end aggregation of rod-like particles. Bernstein and Mazia[14,15] were able to prepare a nucleoprotein from the sperm of sea-urchin which forms long rods approximately 4000 A° long by 200 A° wide. These rods contain DNA, basic protein and a non-histone protein. Since these free particles appear when calcium and magnesium are removed from the chromosome, Mazia postulated that divalent cations (Ca^{++} and Mg^{++}) serve as bridges linking these particles[50]. Ambrose believes that the rod-like particles are linked end to end by hydrogen bonds. Several recent experiments (Eversole and Tatum[26], Steffenson[64,65]) would indicate the presence of low energy bonds like (Ca^{++} and Mg^{++}) linking segments of chromosomes in at least certain species of plants. These bonds are especially interesting when chromosome breakage and crossing over are considered.
3. The structure of chromosomes is basically a spiral one with a large number of helices superimposed on one another. The individual chromofibril consists of a helix, as shown by electron microscopy, and the proposed structure of nucleic acids and proteins is based on a helical arrangement (Feughelman *et al.*[27], Watson[75]).
4. Chromosome reproduction consists of several processes. First the synthesis of DNA and protein must occur. DNA is synthesized during interphase (Swift[69], Thorell[70]); that is, only when chromosome reproduction occurs. (The structure of DNA and possible modes of its replication as well as its probable genetic action will be considered later.) The second process of chromosome reproduction is a replication of the chromofibril. This occurs following DNA and protein synthesis, and in late prophase the chromofibrils are doubled. The next step is the division of the bundle of fibrils into chromatids which will become the daughter chromosomes at anaphase.

In considering the concepts of genetic mechanisms Nanney[55] suggests 2 possibilities. The Master Molecule concept places a special type of material (or master molecule) within the chromosome. This molecule is then the basic structure which directs the specific construction of the various characteristics in the organism. All the other constituents within the cell are of relative unimportance with respect to this master molecule in initiating and controlling the processes of replication. This concept is in effect

the theory of the gene. The second concept he designates as the "Steady State" concept. That is, "an organization of a variety of molecular species which owes its specific properties not to the characteristics of any kind of molecule, but to the functional interrelationship of these molecular species." There is, therefore, inherent in this concept a system of biochemical checks and balances. Since experimental evidence for this second concept is much more difficult to obtain, much of the investigation in this field has favored the former theory. The net result has been in essence to attribute most hereditary traits to the chromosome, leaving the role of cytoplasm and nucleoplasm somewhat in abeyance. Some evidence has been forthcoming in which a certain genetic function is attributable to cellular particles such as the blepharoblasts, kinetosomes and mitochondria (Lwoff[49]). Recent studies (Beale[12], Sonneborn[63]) in the genetic behavior of *Paramecium aurelia* have shown hereditary differences in the transmission of antigenic specificities which are dependent on whether or not a cytoplasmic exchange occurs during conjugation. It would appear that in this system the cytoplasm selects one of the nuclear potentialities for manifestation. These and other studies indicate that there exists a type of hereditary change which differs from the discrete localized effects of mutations in as much as they show a gradual development over an extended period of time. A concept of heredity in which the chromosome, the cytoplasm and the nucleoplasm play their role is quite a likely possibility, but will have to await further investigation.

THE GENETIC ROLE OF DNA. The role of the chromosome, and more specifically that of the nucleic acids and associated structures in cell division and protein synthesis, has received a great deal of attention in the last decade or two. Avery, McLeod and McCarty[9] in 1944, reported that DNA can cause transformation in type specificities of pneumococci. Further evidence has since accumulated (Ephrussi-Taylor[25], Hotchkiss[36]) that would indicate that DNA does constitute the primary genetic material in the pneumococcus. Ephrussi-Taylor demonstrated the effect of transforming DNA (prepared by irradiation) on cultures of reactive pneumococci with the development of streptomycin resistance in a certain proportion of these organisms. Hotchkiss differentiates this process of transformation from the crossing over processes[37]. Crossing over is believed to result from reciprocal exchanges between intact homologous strands, while transformation is due to the nonreciprocal action of a DNA fragment at short range on the DNA of the recipient cell, thereby modifying it or in some way substituting a certain fragment in it. Immediately after this short lived contact between the transforming DNA and the reactive (or competent) cell, a new unit has been formed with a predetermined potentiality. Goodgal and Herriot[30] working with *H. influenzae* have shown that transforming DNA is taken up by these organisms in a reversible form which is sensitive to attack by DNAase or saline washing and an irreversible form which cannot be removed by washing or enzymatic treatment. This irreversible form can be subsequently liberated from the cell by lysing it with lysozyme and once removed in this fashion is sensitive to attack by DNAase.

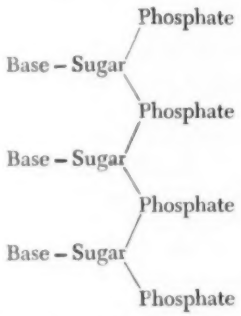
Therefore the transforming factor depends on several steps for its action. It must be able to penetrate the cells and reach the gene at a certain locus in the chromofibril, then displace the DNA or portion of it that was present at this locus, and subsequently must be capable of reproducing itself. Much work has been done in the last decade to identify the chemical nature of this transforming factor and present evidence indicates that it is identical in some of its physical and chemical properties with DNA (Avery, McLeod and McCarty[9], Goodgal and Herriot[30], Hotchkiss[35], McCarty and Avery[52], Zamenhof, Alexander and Leidy[82]).

Further evidence implicating DNA as the primary genetic material has been forthcoming with recent work on the bacteriophage systems. In certain species of bacterial viruses that have been subjected to study, the function of replication has been shown to reside in the DNA portion of the virus (Herriot[33]). Hershey[34] has shown that the material that enters the host when it is infected with a suitable phage, consists of 97% DNA and 3% soluble protein. Kozloff's work with labeled bacteriophage[45] indicates that the bulk of viral protein is not transferred to the progeny. The nucleic acid-portion alone penetrates the host cell and controls the synthesis of both viral nucleic acid and protein. In studying genetic recombination in phage, Levinthal[47] presents some evidence that an interaction occurs between 2 DNA molecules during the course of their replication. He employed a method of molecular autoradiography, in which the radioactive particle (P_{32}-labeled DNA) is surrounded with an electron-sensitive nuclear emulsion so that the passage of a fast electron produces a track composed of exposed silver grains. The activity of the particle can be determined on development of the autoradiograph by observing and counting the number of tracks emanating from the star shaped figure (which is the labeled particle) and by determining the number of stars per unit of emulsion. This method according to Levinthal, is 10^5 times more sensitive than a geiger counter for measuring a localized radioactive label. The results of this experiment indicate that during replication each of the 2 chains of the DNA molecule would be partially copied on one parent and partly on the other, and heterozygous regions would arise if the template switch occurred at a different point on each chain. Doerman, Chase and Stahl[22] and Stent and Fuerst[66,67] have furnished further evidence that genetic material is located in the DNA of a bacterial virus.

Although little if any direct evidence exists in higher forms of life that DNA is the prime genetic substance, it seems quite likely that such evidence will be found in the near future. At present an acceptable hypothesis is that the prime portion of hereditary potentialities can be attributed to DNA rather than the associated proteins.

THE STRUCTURE AND REPLICATION OF DNA. Watson and Crick[76] in 1953 proposed a structure for DNA and a mechanism for its self-duplication. The basic chemical formula, which had already been fairly well established indicates that DNA consists of a very long chain whose core is made up of alternate sugar and phosphate groups jointed together in regular 3′5′ phosphate linkages. A nitrogenous base is attached to each sugar, and only 4 such bases are usually found in DNA. Two of these are purines (adenine and guanine) and the other 2 are pyrimidines (thymine and cytosine). In certain organisms, a fifth base, 5-methyl cytosine occurs in small amounts, and in the T even bacteriophage, Wyatt and Cohen[81] found

that 5-hydroxy-methyl-cytosine occurs instead of cytosine.



BASIC FORMULA OF A SEGMENT OF DNA

The DNA chain is unbranched due to the regular internucleotide linkage. Analysis by physico-chemical means (sedimentation, diffusion, viscosity measurements) gives a similar picture of a long thin fiber of DNA and electron microscopy is an agreement with this concept. Roentgenographic studies (Franklin and Gosling[28], Wilkins *et al.*[79,80]) indicate the existence of 2 chemical chains in the fiber. A structure resembling a spiral staircase has been proposed. The 2 sides of this staircase consist of 2 chains made up of phosphate and sugar groups in which the sequence of the atoms in one chain runs in an opposite direction to the other. The bases lie inside the helix joined together by hydrogen bonds. They are the steps in this spiral staircase (which is coiled in the form of a right-handed helix).

The 2 chains are, therefore, held together by hydrogen bonds between the bases. Watson and Crick[76] develop this structure to show that 2 purines or 2 pyrimidines could not be joined together to form one of these bridges; that is one member of a pair of bases must be a purine, the other a pyrimidine. Assuming that in the physiological state one of the tautomeric forms is preferred, this further restricts the pairing of bases with the result that adenine can only pair with thymine, and guanine only with cytosine. Although the types of pairs are therefore restricted, there is no restriction on the sequence of adjacent pairs in this structure. The replication of DNA can therefore theoretically occur without the prerequisite of specific protein synthesis. They propose that the hydrogen bonds linking the 2 chains will break and the chains will unwind and separate. One chain can then reassume its helical form and serve as a mold for attachment of free nucleotides (by hydrogen bonding). But the problem inherent in this mechanism of duplication is the excessive amount of energy that would be required if the separation of the two DNA chains occurs by unwinding. A large number of turns are required to unwind such a long polynucleotide chain and for each turn to be unwound, the whole mass of the DNA molecule has to rotate once completely around its axis. Delbruck and Stent[21] report on calculations made by Levinthal and Crane on the mechanical aspects of unwinding in which they arrive at an energy requirement of 150 cal. per mole of replicated chain link (if DNA was a straight rod). They further suggest that the coiled DNA will rotate like a speedometer cable, assuming that the process of replication occurs simultaneously with the unwinding of the DNA molecule. That is, replication begins to occur as soon as one end of the DNA molecule starts to unwind, and continues along each arm while the rest of the molecule is unwinding into its 2 separate chains. Other mechanisms of unwinding have been proposed (Delbruck[20], Platt[58]) and at present there is no definite evidence which can satisfactorily resolve this problem.

In the aforementioned duplication

scheme the specific pairing between adenine with thymine and guanine with cytosine (which is the means of achieving a specificity in replication) was based on the assumption that in the physiological state, one of the tautomeric forms of these bases is preferred to the others. However, should a base occur in another tautomeric form at the moment when the complementary chain is being synthesized, a mechanism for spontaneous mutation is therefore indicated, assuming that such a spontaneous mutation is due to a change in base sequence.

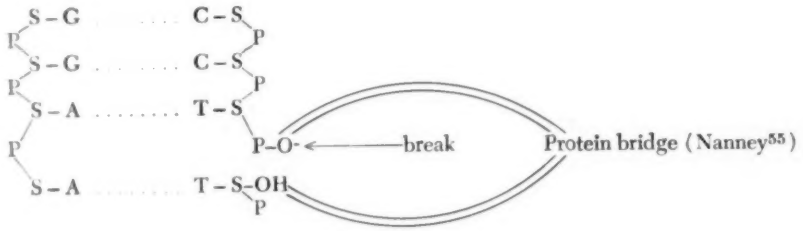
DNA AND PROTEIN SYNTHESIS. Protein synthesis has been demonstrated in the nucleus and cytoplasm of cells (Allfrey, Daly and Mirsky[2,3], Allfrey, Mirsky and Osawa[4], Siekewitz[61]). These investigations were carried out by studying labeled amino acid uptake in preparations of isolated nuclei and cytoplasmic particulates and they indicate that a synthesis rather than a nonspecific exchange reaction occurs. If the template mechanism of protein synthesis is accepted (and much of the present day experimental evidence apparently favors this concept) then such a macromolecule must be one which is universally distributed and synthesized by a mechanism which insures that the sequence of template elements is specified and maintained with accuracy. Three molecules which can be considered to be most suitable for this role are DNA, RNA and protein. The latter can be eliminated, since if protein is the template then all proteins must either be capable of self-duplication or, if certain proteins function as the template in synthesizing all the remaining proteins, there is still the problem of making these specific protein templates. It is difficult to accept the concept of certain proteins being able to act as catalysts in the formation of many other proteins and also having the ability of catalyzing their own synthesis.

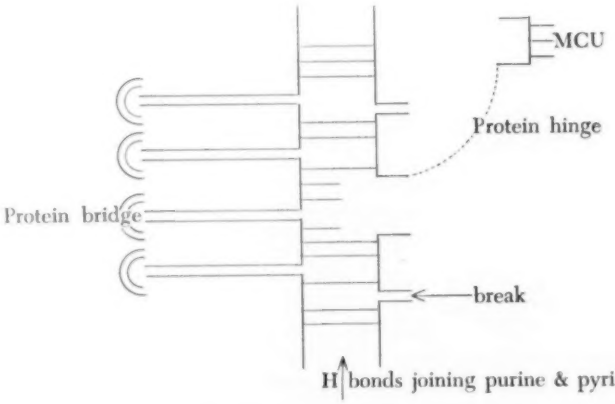
In considering the possibility that DNA serves as the template for protein synthesis, the utilization of anucleate systems is perhaps one of the most direct methods of obtaining information. The results of such investigations (Brachet[16], James[42], Mazia and Prescott[51]) show that in these systems (although there is some loss of RNA), the ability to incorporate labeled amino acids into protein is still maintained. DNA is, therefore, not necessary in these systems for protein synthesis to occur. Further evidence has been forthcoming in which interference with DNA synthesis by Roentgen irradiation and ultraviolet light is not accompanied by inhibition in the formation of protein (Abrams[1], Baron, Spiegelman and Quastler[11]). This data would, therefore, tend to mitigate against the assumption that DNA acts as the template.

Aside from a process of exclusion there is a good deal of data which more than implicates RNA as the template in protein synthesis (Allfrey, Daly and Mirsky[2], Gale and Folkes[29], Halvorson and Jackson[32], Webster and Johnson[77]). Gale and Folkes[29] observed that the addition of intact bacterial RNA will restore the ability of bacterial extracts (previously treated with ribonuclease) to incorporate amino acids. Webster and Johnson[77] have recently reported that intact RNA is apparently not necessary in such systems. A mixture of 4 nucleosides obtained from RNA seems to be more effective in promoting amino acid incorporation. (If deoxyribonucleosides are employed instead of nucleosides derived from RNA, no effect is obtained). Studies on the synthesis of induced enzymes in yeast (Holvorson and Jackson[32]) showed that an ultraviolet dose that inhibited RNA metabolism by 22%, suppressed the enzyme

formation by 95%. In general, it is therefore valid to assume that protein synthesis is unable to proceed in the absence of RNA or RNA synthesis. It is then not difficult to accept the corollary that RNA does function as the template in protein formation. One can further extrapolate this concept and conclude from the foregoing discussion that the prime genetic information is stored within the DNA molecule (DNA is the gene) and the DNA deoxyribose sugar(s) which are in turn linked through phosphate (p) diesters.

An occasional break in the diester linkage is postulated; these breaks in the two chains being staggered relative to one another. The unit between breaks is called the "minimum chemical unit" (MCU) and some of the protein associated with DNA in the chromosome is believed to act as a bridge between these DNA minimum chemical



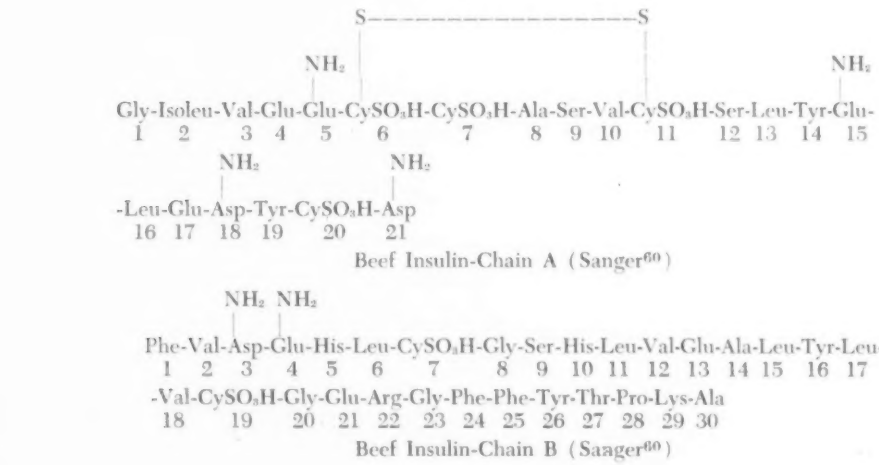


is capable of transmitting this information to the template RNA in order to ensure proper protein synthesis and specificity. De Busk[18] presents a model for intracellular transfer of DNA (gene specificity based on Dekker and Schachmans[19] modification of the Watson and Crick DNA molecule structure[76]. As previously described, it consists of chains of specific purine and pyrimidine bases (A–T & G–C) paired by hydrogen bonding, attached to units. The first step in the transfer of specificity occurs with the breaking of the relatively weak hydrogen bonds and removal of the MCU, with a resultant gap in one side of the 2 chained helix.

As shown in the above figure, the MCU is actually retained by protein hinge attachments (dotted line). The gap is filled by ribose nucleosides which are positioned through hydrogen bonding in specific sequences. These

nucleosides are then phosphorylated and esterified through 3′–5′ linkages, resulting in a unit of RNA whose structure is therefore determined by the DNA molecule. This RNA template can then be ejected from the DNA molecule and the hinged MCU returned to its original position.

SPECIES DIFFERENCES IN PROTEIN STRUCTURE. The extensive investigations by Sanger and associates[60] on the structure of insulin have led to complete structural formulas for the insulins of beef, sheep, and pig. Their method in essence consisted of first determining the amino acid composition of insulin by qualitative techniques. An amino acid that can be assigned to one end of a chain is that one which bears a free amino group. This N terminal amino acid residue can be distinguished from the other amino acids by certain chemical reactions. These involve the reactions of 1,2,4 fluorodinitrobenzene with amino groups to form yellow dinitrophenyl (DNP) compounds. Hydrolysis of DNP protein yields DNP derivatives of the N terminal amino acids. DNP glycine and DNP phenylalanine in equivalent amounts are found in a hydrolysate of DNP Insulin, thereby indicating that the molecule is composed of 2 polypeptide chains—a glycyl chain (Fraction A) and a phenylalanyl chain (Fraction B). By a series of experiments in which the structure of each of the many peptides obtained by partial hydrolysis of chain A and B of the insulin molecule was elaborated, Sanger was able to deduce the complete sequence of amino acid residues in each of these chains. He presents the following formula for beef insulin:


S——————————S
NH₂
NH₂
Gly-Isoleu-Val-Glu-Glu-CySO₃H-CySO₃H-Ala-Ser-Val-CySO₃H-Ser-Leu-Tyr-Glu-
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
NH₂
NH₂
-Leu-Glu-Asp-Tyr-CySO₃H-Asp
16 17 18 19 20 21
NH₂ NH₂
Phe-Val-Asp-Glu-His-Leu-CySO₃H-Gly-Ser-His-Leu-Val-Glu-Ala-Leu-Tyr-Leu-
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
-Val-CySO₃H-Gly-Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Pro-Lys-Ala
18 19 20 21 22 23 24 25 26 27 28 29 30

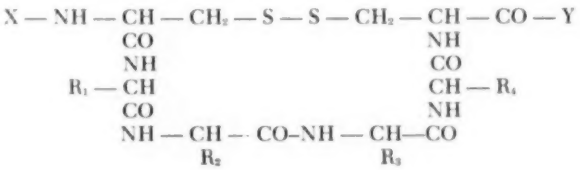
Beef Insulin-Chain A (Sanger[60])

Beef Insulin-Chain B (Saager[60])

The complete sequence of 30 amino acid residues in chain B is identical for beef, sheep and pig insulin. The same is true in chain A except for residues 8,9,10 which lie within the intrachain disulphide loop. In sheep insulin the sequence is alanine-glycine-valine at the 8,9,10 position, while in pig insulin it is threonine-serine-isoleusine. In comparing them with beef insulin in which the 8,9,10 sequence is alanine-serine-valine, it is evident that the genetic information that predetermines the nature and type of the protein to be produced must be extremely accurate and well localized to be so specific.

The disulphide intrachain loop pres-

ent in insulin, has also been found in the smaller polypeptide hormones oxytocin and vasopressin by du Vigneaud and his associates[23,24]. The structure of these 2 hormones is shown in the following graphic form, and is compared to the 3 insulins.



Nature of attached residue(s) at position

	X	R_1	R_2	R_3	R_4	*Y*
Beef Insulin	val-glu-gluNH_2	cyS	ala-ser		val	ser-leu-tyr
Pig Insulin	val-glu-gluNH_2	cyS	thr-ser		isoleu	ser-leu-tyr
Sheep Insulin	val-glu-gluNH_2	cyS	ala-gly		val	ser-leu-tyr
Oxytocin	H	tyr	isoleu	gluNH_2	aspNH_2	pro-leu-glyNH_2
Arg. Vasopressin	H	tyr	phe	gluNH_2	aspNH_2	pro-arg-glyNH_2
Lys. Vasopressin	H	tyr	phe	gluNH_2	aspNH_2	pro-lys-glyNH_2

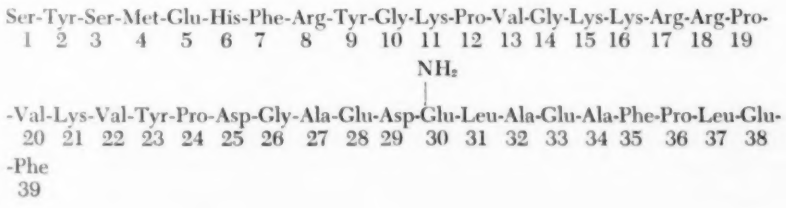
It is again noteworthy that oxytocin and vasopressin differ in 2 amino acid residues and yet exert different physiological actions. The known biological activity of oxytocin is the stimulation of uterine contraction, and vasopressin acts as an antidiuretic and peripheral vasoconstrictor; both hormones are elaborated by the posterior pituitary gland. (The presence of the unusual disulphide ring in these various hormones is also of some interest since it might bear some special relationship to their physiological activities.)

Structural sequences for several of the corticotrophins have been reported. Pig corticotrophin consists of a single chain of 39 amino acid residues (Bell[13], Howard *et al.*[38]).

The sequence for pig corticotrophin A and sheep corticotrophin have also been derived (Li *et al.*[48], White and Landmann[78]) and they are identical with the sequence for pig corticotrophin except for residues 25–33.

Here again there is very little difference between the three; in residues 25–30 while the order differs the composition is the same, while in residues 31–33 only sheep α corticotrophin differs from the other 2 and this difference is just in one amino acid.

The structural formulas of the cytochromes with the exception of Cytochrome C (and only a partial structure has been defined), have not yet been characterized. They have until recently defied all attempts at isolation and purification, probably because


Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Tyr-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
NH₂
-Val-Lys-Val-Tyr-Pro-Asp-Gly-Ala-Glu-Asp-Glu-Leu-Ala-Glu-Ala-Phe-Pro-Leu-Glu-
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38
-Phe
39

they are part of the mitochondrial complex of insoluble enzymes. A 12 amino acid sequence in the immediate vicinity of the hematin prosthetic group has recently been proposed for cytochrome C. (Tuppy and Bodo[71], Tuppy and Paleus[72]). The Sanger DNP method for characterizing the amino acid residues was employed by these investigators; the hematin portion having been previously removed by Paul's silver-splitting technique. The hemopeptides from cytochrome C of horse, beef, pig and salmon have the identical structure (as shown below).

Residue No.	*25*	*26*	*27*	*28*	*29*	*30*	*31*	*32*	*33*
Pig β Corticotrophin	Asp	Gly	Ala	Glu	Asp	Glu NH_2	Leu	Ala	Glu
Pig Corticotrophin A	Gly	Ala	Glu	Asp	Asp	Glu	Leu	Ala	Glu
Sheep α Corticotrphin	Ala	Gly	Glu	Asp	Asp	Glu	Ala	Ser	Glu

1 2 3 4 5 6 7 8 9 10 11 12
-Val-GluNH_2-Lys-Cy-Ala-GluNH_2-Cy-His-Thr-Val-Glu-Lys-
S —Hematin— S

The hemopeptide from chicken cytochrome C differs from the others by virtue of the fact that it contains serine in place of alanine at residue 5.

Ingram's work on several of the abnormal hemoglobins[40] demonstrates that the only difference between the molecules of hemoglobin A (normal) hemoglobin S (sickle cell anemia) and hemoglobin C (hemoglobin C anemia) resides in a single amino acid residue. In the short section (9 amino acid peptide structure) of the hemoglobin molecule that Ingram has reported, he gives the following structure for hemoglobin A.

his - val - leu - leu - thr - pro - glu - glu - lys

Hemoglobin S differs from this structure in the substitution of valine for glutamic acid (starred), and in hemoglobin C, lysine is present instead of this glutamic acid residue. Previous work (Banks, Scott and Simmons[10], Itano[41], Motulsky, Paul and Durrum[54], Neel *et al.*[56,57], Silvestroni and Bianco[62]) has indicated that these defects are of an hereditary nature, traceable to the action of a single genetic mutation which causes the synthesis of a hemoglobin chemically different from the normal form. The individual with sickle cell anemia is homozygous, while the individual harboring the sickle cell trait is heterozygous.

With the stimulus provided by Sanger's monumental work on the insulins, it is not unreasonable to expect the elaboration of the structural formulas of many more proteins in the near future. Several conditions involving disorders in metabolism with known hereditary tendencies, have recently been subjected to intensive biochemical study. In these disease entities, there is now evidence that the metabolic disorder is due to a lack or deficiency in a specific protein (that is, an enzyme) in the individual harboring the disease and this lack is apparently predetermined on a genetic basis.

In congenital galactosemia, Kalckar and his associates[8,43,44] have shown that the red blood cell and liver in such individuals are lacking in the enzyme galactose-1-phospho-uridyl transferase with the resultant accumulation of galactose-1-phosphate in these cells. Galactosemia is believed to be inherited as a recessive gene, and it is suggested that there are at least 2 mul-

tiple alleles involved. If A is the normal gene and A′ the mutant gene that affects galactose-1-phosphate metabolism (on the basis of a genetic block), then a third allele A″ may be present which causes another type of manifestation, and when combined with A′ will aggravate the disorder in galactose metabolism. They are both inherited as recessive characteristics. Such a mechanism is indicated by the finding of an elevation in galactose tolerance tests in one or both parents of a child born with galactosemia. Kalckar further assumes that at least 4 genes are required for normal function of the transferase enzyme. He bases this assumption on the work of Kurahashi[46] who found that 4 different mutants of *E. coli* were lacking in galactose-1-phospho uridyl transferase, and Morse, Lederberg and Lederberg[53] showed that there are alterations in different though closely related genes in these 4 mutant strains.

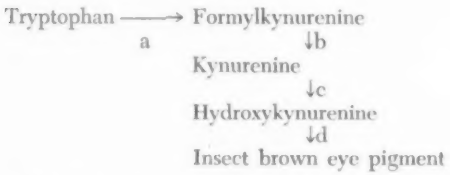
The extensive studies by the Cori's[17, 39] on the glycogen storage diseases give further evidence of a genetic block causing a deficiency in specific enzymes. In the hepatic type of von Gierkes' disease, they showed that there is almost a complete lack (in some cases) of glucose -6- phophatase in the liver and kidney, resulting in glycogen storage in these organs. In the generalized form of glycogen storage disease there is evidence of a lack of the debranching enzyme amylo -1,6- glucosidase, leading to a accumulation of abnormal glycogen with short outer chains.

Two other diseases can be cited, which indicate a similar genetic block although the disorder in the metabolic pathway and the specific enzyme involved have not as yet been characterized. Alcaptonuria which is probably inherited as a single recessive gene, is a metabolic disease in which the urine of the individual affected turns black on exposure to air. Homogentisic acid (2,5 dihydrophenyl acetic acid) is responsible for this phenomenon. Gross[31] found that this acid disappeared when normal serum was added, indicating that the enzyme or enzymes responsible for the metabolism of homogentisic acid to acetoacetic acid are lacking in the individual with alcaptonuria. Idiopathic methemoglobinemia is another rare metabolic disease which is probably inherited as a recessive gene. In the normal individual the red cells contain approximately 1% of their hemoglobin in the form of methemoglobin. A reducing system is present in these cells which keeps most of the iron in the hemoglobin molecule in the reduced (Fe^{++}) state. Oxidizing agents will markedly increase the amount of methemoglobin but the red cell will rapidly reduce it to hemoglobin. The individual with methemoglobinemia is apparently lacking an active regenerating system to reduce methemoglobin. The flavoprotein electron carrier is probably deficient in quantity or quality in this individual.

A more elegant indication of the presence of such genetic blocks can be found in the study of the intermediary metabolism of amino acids in bacteria and insects (Wagner and Mitchell[73]). The work relating to the inheritance of brown pigment in the eye of a fruit fly *Drosophila melanogaster* is particularly revealing. There are 4 known recessive nonallelic genes that will block the formation of brown pigment. These are vermillion (v), cinnabar (cn), scarlet (st), and cardinal (cd). Eye anlage can be transplanted from the larvae of a population of flies homozygous for v, into the abdomen of host larvae homozygous for another gene, for example cn/cn. In analyzing the results it was found that v/v anlage developed brown pigment in the cn host,

but cn/cn larvae eyes were unable to develop this pigment in a v/v host. This suggests that the mutants differ in the kind of pigment intermediates that they are able to synthesize. These intermediates have been isolated, identified and synthesized.

A metabolic scheme has been proposed in which tryptophan is an important metabolite for the formation of insect brown eye pigment.

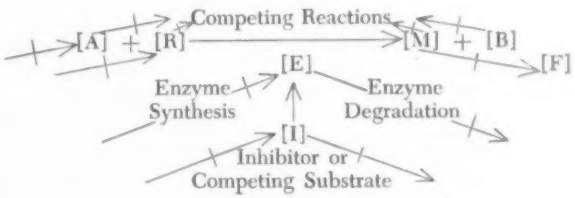


In the v/v mutant the block exists at a and b while in the cn/cn strain the block occurs at c. Therefore, if v/v eye anlage are grown in cn/cn hosts, the host can supply the formlkynurenine and kynurenine to the v/v eye and it can then proceed with the production of pigment along the lines outlined above. But if cn/cn anlage are grown in v/v hosts, the host is unable to supply the hydroxyknurenine required by the cn/cn strain, and no pigment is produced. Further confirmatory evidence relating to the occurrence and location of these genetic blocks is shown by the development of pigment in v/v strains if the larvae are fed formylkynurenine and kynurenine. An accumulation of tryptophan in the v/v adult mutant and kynurenine in the cn/cn adult mutant supplies more evidence that these blocks do exist.

Although they may appear to be a matter of a simple block between reactant R to form essential metabolite M, with the genetic block being caused by a deficiency of an enzyme to catalyse this reaction, these genetic blocks are actually much more complex. The following equation indicates some of the possible loci where a block could occur, resulting in a lack or absence of the necessary functioning metabolite (F). (Derived from Wagner and Mitchell[74].)

The cross bars indicate loci where a block might occur which could result in the relative or absolute deficiency of a functioning metabolite (F) such as hydroxykynurenine in the cn/cn strain of Drosophila.

It can be seen that the reaction rate depends on the approximate steady state concentration of the reactants A & R, and the products M & B as well as on the concentration of the enzyme



E. The concentration in turn depends on the relative rate of formation of A, R & E, and on the relative rate of diversion of A, R, M, and B into side reactions, and on the formation of an inhibitor or competing substrate (I) and its rate of degradation. A genetic block, depending on where it occurs, is therefore itself a characteristic metabolic pattern. The resulting phenotype expression (for example lack of brown pigment) will depend just as much on the pattern that existed prior to mutation as it does on the pattern that develops following the mutation.

A mutation can therefore give rise

to a single or even multiple effects. These may vary in severity from a condition such as alcaptonuria which does not appear to be harmful to the organism to a more serious disease such as galactosemia, or to a disease which may be fatal such as sickle cell anemia or one of the glycogen storage diseases. It is also apparent that genetic aberration can predetermine (within the same species) a protein molecule in which only one or two amino acid residues are changed (for example, hemoglobin S or C). It is also becoming evident that protein differences between species may be determined by subtle changes within the molecule as shown in the various insulins, cytochromes and hormones. Perhaps such changes will eventually be found to have determined many of the pathways of evolution that have occurred. Stetten[68] has in fact indicated this possibility in his studies on the metabolic defect in gout. He fed labeled nitrogen (in the form of N^{15} glycine) to 3 gouty subjects and found a much greater elimination of nitrogen in the urinary uric acid fraction (about 0.5% in 10 days) as compared to the normal individual who excretes less than 0.15% as uric acid. In man the usual route for excretion of nitrogen is in the form of urea, about 20% in the first 24 hours and up to 50% within 10 days. In the gouty individual there was no change in the amount of N^{15} eliminated as urea. Stetten suggested that in these people a large proportion of dietary glycine is used for the synthesis of uric acid, much of which is then excreted in the urine. This, over a prolonged period of time, may account for the increase in size of the miscible pool of uric acid which occurs in gout. A larger proportion of glycine is, therefore, deflected toward uric acid synthesis (as in the bird or reptile) while in the normal individual most of the dietary glycine is probably utilized in the synthesis of purines. The gouty individual has, therefore, in a sense regressed to the avian pathways with respect to uric acid metabolism. Instead of a ureotelic animal, he is developing into a uricotelic animal such as the bird or reptile. In these animals, glycine is utilized to form uric acid, and nitrogen is excreted chiefly in the form of uric acid. This is an example of a mutational regression, and it is not at all inconceivable that more evidence will be forthcoming which will give us greater insight into the mechanism of evolution. As has been shown in this discussion, a very small change within a relatively large protein molecule, determined genetically, can lead to severe physiological and biochemical disturbances within the organism. It is possible that similar changes in a gene or group of genes can lead to extinction of a strain or even a species. Such lethal mutants have in fact frequently been produced in bacteria and insects. A change at a different locus can serve to strengthen the population with respect to its survival. This has been accomplished experimentally with the transforming principle (transforming DNA) in pneumococci, and is as frequently encountered clinically as the development of drug resistance by an organism. It is therefore quite reasonable to assume that a series of changes in genes will function in a similar manner biochemically and lead to the development or evolution of a new species of animal. As more information is forthcoming, it will quite likely continue to show the close relationship of protein molecules from different species and further indicate the biochemical pathways that have been developed to give rise to various pathways in evolution.

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(Interlingua on page 417)

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EFFECTS OF COMBINATIONS OF PSYCHOPHARMACOLOGIC AGENTS*

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IT is becoming increasingly evident from clinical, neurosurgical, electrophysiological, and pharmacological studies that alteration in activity of different brain regions may modify behavioral reactions in animals and man. The observations that excitation, hallucinations, pacification, sleep, and coma may be experimentally induced by various procedures would appear to support the concept that certain brain regions have specific functions with regard to psychological organization of an individual and that modification of the activity of such regions may alter behavioral reactions (Brady[4], Schreiner and Kling[9], Spiegel, Miller and Oppenheimer[10]). The varied responses induced by the administration of drugs having different chemical structures suggests specific biochemical differences in various brain regions so that some may be more responsive to a particular agent than are other cerebral structures (Bradley and Elkes[3]).

The exact reason for the selective action of various drugs is not known; however, variations in biochemical composition of the different regions of the brain (enzymes, co-enzymes, and neurohumors) have been demonstrated and may be the most likely explanation (Costa and Aprison[5], Vogt[11]). It is possible that local differences in cerebral circulation may in some cases be an alternate explanation for differences in the activity of various drugs. Whatever the mechanism, since the selective brain regions are interconnected, abnormal behavior may result not only from disintegrated activity of specific centers, but also from impairment of integration of neuronal impulses at various levels.

Recent attempts at therapy of emotional disorders have included the administration of individual neuropharmacological agents presumed to affect primarily specific subcortical centers (Gordon[6]). There is evidence to suggest that the phenothiazines primarily affect the reticular formation or its sensory input, meprobamate influences the thalamus, and the rauwolfia alkaloids alter the activity of the hypothal-

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amus (Berger[1], Bradley[2], Himwich[7], Killam and Killam[8]). In this connection, a limited locus of action of these drugs is not clearly evident from their clinical effects, since all of them in sufficient doses will control excessive psychomotor activity or induce sleep. This observation may well depend upon the interconnections between the various subcortical centers and the cortex and suggests that modulation or reduction of neuronal activity in any particular brain area (if hyperactive) might be expected to have a generalized influence, or that with increasing doses the activity of additional brain areas may also be influenced or modified.

Although the use of individual ataractic agents has proved highly successful in the management and improvement in accessibility of disturbed patients (Gordon[6]), many such individuals may benefit little or not at all, or are affected only by doses so large that a highly undesirable degree of lethargy or somnolence is induced, prohibiting patient cooperation in rehabilitation efforts. In view of the presumably different sites of action of meprobamate and promazine, and in consideration of the possibility of potentiation by their simultaneous administration, a comparative study of their clinical effectiveness alone and in combination was conducted. An additional factor influencing selection of these two drugs was the relative infrequency of side effects attendant upon their individual administration.

Method. The subjects of the present study were disturbed mentally retarded and juvenile delinquent subjects confined to a primarily custodial institution remote from a teaching-medical environment and severely limited as to psychiatric and rehabilitative programs because of budgetary limitations and personnel recruitment problems. During the preceding several years of their confinement, most of these subjects had received for purposes of facilitating their management various doses of meprobamate or promazine as well as other agents.

In the present study, 94 agitated mentally retarded inmates and 99 juvenile delinquent subjects ranging from 13 to 18 years of age received combined doses in varying proportions of meprobamate and promazine. Evaluation of the relative effectiveness of these drugs was based upon daily reports enumerating activities such as attempts at self-mutilation or suicide, destruction of property, elopement, seclusion because of belligerence or combativeness, and extent of participation in vocational, academic, and recreational facilities. Slight changes in behavior or incidence of social alterations, as mentioned above, of less than 25% were arbitrarily considered to represent expected spontaneous swings in behavior and, therefore, to be probably unrelated to drug therapy. More evident and reasonably sustained behavioral improvement and reduction in antisocial incidents of 25 to 50% were considered indicative of moderate improvement, while immediately obvious behavioral improvement and a 50% or better reduction in undesirable activities were classified as marked improvement. Most of the patients received 25 mg. of promazine with 200 mg. of meprobamate 3 times daily. Where results were not considered satisfactory, the doses of these drugs in the same proportion were increased so that in a few instances the total daily doses consisted of 225 mg. of promazine and 1800 mg. of meprobamate before significant improvement was effected. In 2 cases, daily doses up to 400 mg. of promazine combined with 3200 mg. of meprobamate were given before therapy was abandoned. In only one instance was the total daily dose of the drug combination as small as 50 mg. of promazine and 400 mg. of meprobamate. The study was conducted over a period of from 2 to 7 months. All patients were observed closely for clinically-evident side effects associated with phenothiazine or meprobamate administration, and where any suspicion of these was aroused, hemogram and liver function studies were performed. In a separate series of 15 patients who were known epileptics, the combination (25 mg. of promazine and 200 mg. of meprobamate, t.i.d.) was administered in order to determine whether there was increased frequency of seizures.

In order to determine the relative effectiveness of the two drugs, alone and in combination, on alertness, 7 patients were closely observed over periods of 8 hours after a con-

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trol phase and after single doses of 1200 mg. of meprobamate; after single doses of 150 mg. of promazine; and after a single dose of a combination of 150 mg. of promazine with 1200 mg. of meprobamate. A 3-day interval intervened between the administration of the drugs to insure cessation of their specific pharmacological effects.

Results. In the study performed to determine whether these drugs in combination exerted synergistic effect, it was found that 1200 mg. of meprobamate alone had no appreciable effect on alertness, 150 mg. of promazine produced slight to moderate reduction of activity, while the combination of both drugs in the same doses had a marked somnifacient effect beginning one-half hour after administration and persisting for 4 to 6 hours.

Table 1 presents the results of administering the combination to 76 disturbed mentally retarded and 99 juvenile delinquent subjects. In all patients, 45% showed marked improvement in behavior attributable to doses of promazine and meprobamate up to 225 mg. and 1800 mg. daily, respectively; 44% showed moderate improvement with these or lower doses of the combination; and 11% showed no demonstrable improvement. In addition, 3 of the subjects showed no improvement even when given considerably higher doses. Forty-six per cent of the subjects who exhibited marked or moderate improvement responded to 75 mg. of promazine and 600 mg. of meprobamate per day. The second and most frequently effective dose of the drug combination consisted of twice the amounts just mentioned and were administered to 53 subjects (27%), all except one of whom showed moderate to marked improvement. In 18 other refractory cases not included in the table, the doses of promazine and meprobamate were individualized instead of holding to a 1 to 8 ratio, with greater proportions of promazine administered. Here, also, it was found that amounts of meprobamate exceeding 1800 mg. daily were unlikely to be effective, although doses of promazine as high as 450 mg. daily were sometimes required. Thirteen of these refractory cases showed improvement with a promazine-meprobamate ratio of 1 to 4, of whom 8 responded to a daily dose of 300 mg. of promazine with 1200 mg. of meprobamate.

The combinations of drugs when administered to 15 epileptics in daily doses as high as 225 mg. of promazine with 1800 mg. of meprobamate, along

TABLE 1.—RESPONSE TO COMBINATIONS OF PSYCHOPHARMACOLOGIC AGENTS IN DISTURBED MENTALLY RETARDED AND JUVENILE DELINQUENT SUBJECTS

Dosage		*Behavioral Improvement in Mentally Retarded Subjects*			*Behavioral Improvement in Juvenile Delinquent Subjects*		
Promazine mg./day	*Meprobamate mg./day*	*Marked*	*Moderate*	*None*	*Marked*	*Moderate*	*None*
50	400	1					
75	600	23	16	1	18	23	7
100	800	2	1				
150	1200	9	14		13	16	1
175	1400	1	1				
225	1800	3	2		8	4	8
300	2400			1			1
400	3200			1			
		Total Subjects					
		39	34	3	39	43	17

with the usual anticonvulsant therapy, over a period of 4 months did not increase the incidence of seizures. The only undesirable side effect noted in this study was an allergic reaction in a patient who had previously shown this reaction to promazine alone and to three other phenothiazine derivatives.

Discussion. The results of this study demonstrate that promazine and meprobamate in combination are synergistic in action and potentiate one another's effect on overt disordered behavior. According to the criteria used, the majority of the patients showed moderate to marked reduction of their antisocial activities with relatively low doses of combinations of each drug. This was particularly impressive in view of the fact that meprobamate alone in considerably higher doses had previously been found to be essentially ineffective in severely disturbed subjects, while effective doses of promazine, frequently much higher than in the combination, have produced some undesirable lethargy and somnolence.

It must be emphasized that the combination of drugs not only facilitated institutional management of these patients by reducing antisocial behavior, but also rendered them more tractable and the juvenile delinquents more accessible to rehabilitative efforts. The experience herein obtained indicates that the most frequently effective proportion of these drugs in severely disturbed subjects is a 1 to 8 ratio of promazine and meprobamate, and the most frequently effective daily dose is 75 mg. and 600 mg., respectively. In a moderate number of cases, double these doses were required. From the results, it appears unlikely that where combinations of promazine are used, daily doses of meprobamate in excess of 1200 mg. contribute little to the therapeutic effect. On the other hand, daily amounts of promazine of 300 to 450 mg. may occasionally be required in refractory cases.

Inasmuch as meprobamate is inherently of low order of toxicity, it would appear permissible to administer larger than necessary quantities in a fixed-drug combination for the sake of arriving at a satisfactory behavioral response.

The results of this study not only demonstrate a practical application of multiple drug therapy, but also present certain theoretical implications. The potentiation of individual effects demonstrated by combined administration of meprobamate and promazine may be attributed to different loci of activity or receptor sites for the two drugs, as has been recently postulated from neurophysiological data. It is probable that this potentiation may be explained by modulation or inhibition of afferent or efferent impulses traversing pathways common to separate receptor sites of each drug. It is also possible that there may be modulation or inhibition of impulses via pathways which are separate, that is, not common to the receptor site of either drug.

More specifically, although neurophysiological and anatomical information presently available indicates that the reticular formation and diffuse thalamic projection system are integrated to form the mesodiencephalic activity system, it is conceivable that either of the former may send to, or receive from, the sensory cortex independent impulses. In view of the interdependence of various cerebral areas and systems because of interneuronal connections and integration, it should not be surprising that activity of a single drug acting on a presumably specific subcortical locus may have a clinical effect similar to that of a chemically different drug acting in a different region. Even the cortex, which in

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the final analysis is probably responsible for receiving, directing, and organizing the functional cerebral activities, must be at least indirectly influenced by drugs having their pharmacological effects primarily upon lower brain areas. Certainly the reduction of psychomotor activity attendant upon the use of the various ataractic drugs supports the concept of cortical organization of impulses traveling the final common pathway.

Summary and Conclusions. Combinations of promazine and meprobamate were administered to 94 disturbed mentally retarded and to 99 juvenile delinquent subjects who presented difficult problems of management in a custodial institution. Control of abnormal behavior was achieved in the majority of persons in which similar doses of meprobamate alone had been ineffective and in whom larger doses of promazine alone produced lethargy and stupor.

Previous experience with these drugs, used separately, disclosed that meprobamate in similar quantities was ineffective in these disturbed subjects, and that in many instances the larger doses of promazine necessary for control produced such lethargy and stupor that rehabilitative efforts in juvenile delinquent subjects were difficult.

The combination of drugs permitted the use of doses of promazine which were effective although significantly less than required alone and not attended by undesirable somnolence. The theoretical implication of the synergistic activity on the basis of different sites of action of the two drugs is discussed.

In a separate series of 15 epileptics, the administration during a 4-month period of the promazine-meprobamate combination in addition to the usual anticonvulsant therapy did not increase the incidence of seizures.

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SUMMARIO IN INTERLINGUA

Le Effectos de Combinationes de Agentes Psychopharmacologic

Combinationes de promazina e meprobamato esseva administrate a 94 disturbate retardatos mental e 99 delinquentes juvenil qui omnes presentava difficil

problemas de maneamento in un institution custodial. Le correction del anormalitates comportamental esseva effectuate in le majoritate del subjectos in qui simile doses de meprobamato sol habeva essite inefficace e in qui plus grande doses de promazina sol habeva producite lethargia e stupor.

Le previe experientia con le duo drogas in uso individual ha revelate que meprobamato in simile quantitates es inefficace in iste disturbate subjectos e que in multe casos le plus grande doses de promazina que es requirite pro obtener le desirate effecto resulta etiam in tal lethargia e stupor que le effortios rehabilitatori in delinquentes juvenil es multo impedite.

Le combination del drogas rendeva possibile le uso de promazina in doses que esseva efficace sed significativemente plus basse que illos requirite quando promazina es usate sol, e le combination non resultava in indesirabile somnolentia. Es discutite le implicationes theoric del activitate synergic del duo drogas super le base del these de differente sitos de action pro illos.

In un serie separate de 15 epilepticos, le administration del combinatioin de promazina con meprobamato durante un periodo de 4 menses como supplemento al usual therapia anticonvulsori non resultava in un augmento del incidentia de attaccos.

SUMMARIO IN INTERLINGUA

(See page 397 for original article)

Chimia, Hereditate, e Morbo

In iste articulo, un revista e discussion del pertinente principios e considerationes genetic es presentate. Es citate le factos que supporta le these del rolo de acidos nucleic in le division del cellula e in le synthese de proteina. Attention special es prestate al rolo de acido disoxyribonucleic e acido ribonucleic como factor de transformation. Le rolos respective del duo acidos in le synthese de proteina es considerate, e le structura e postulate mechanismos del replication de acido disoxyribonucleic es presentate.

Le labores de Sanger con respecto al determination del structura de insulina es summarisate brevemente, e le differentiation del structura de iste molecula proteinic secundo differente species es signalate. Similemente, le sequentias structural de plure hormones—per exemplo oxytocina, vasopressina, e le corticotrophinas—es discutite ab le puncto de vista de lor differentias in differente species. Le relativemente minime alterationes del molecula de hemoglobina que suffice a resultar in sever entitates pathologic es delineate.

Le base chimic de blocos genetic es considerate con referentias special al blocos de enzyma que occurre in entitates pathologic como congenite galactosemia, le morbos de immagasinage de glycogeno, alcaptonuria, e methemoglobinuria e in le metabolismo intermediari de bacterios e insectos.

Le paragraphos final discute le signification del chimia in le processo del evolution.

DIABETIC NEUROPATHY FOLLOWING STRESS SITUATIONS

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Poor diabetic control over a prolonged period of time has been generally assumed to form the pathogenetic background for diabetic neuropathy (Duncan[1], Goodman[6], Joslin *et al.*[10], Martin[13]). This dictum has recently been challenged by the observations that the neuropathy may be the initial clinical manifestation of diabetes unaccompanied by any symptoms of hyperglycemia and glycosuria (Ellenberg[2], Sullivan[17]) and that the neuropathy may be paradoxically precipitated following the control of diabetes by diet (Rundles[16]), insulin (Ellenberg[3]), or tolbutamide (Ellenberg[4]). The present report deals with another deviation from the poor control hypothesis, namely the occurrence of diabetic neuropathy following stress phenomena.

There have been sporadic references in the literature to the fact that neuropathy in diabetes may follow episodes of stress occurring incidentally in the course of diabetes. For example, in the large series of Rundles[16] are included cases of neuropathy following upper respiratory infection, influenza, pneumonia, pyogenic infection, hyperthyroidism, diabetic acidosis, coma, and surgery. Incidental details of case reports of Rudy[15] indicate that in one patient the neuropathy followed herniorrhaphy, in another after control with insulin, another after coma and a fourth after bronchopneumonia; significantly these protocols indicated good control of the diabetes preceding the onset of both the stress situation and the neuropathy. Jordan[9] recorded a case of neuropathy following extraction of an abscessed tooth and 2 cases occurring after diabetic coma.

This paper presents a group of cases illustrating the onset of neuropathy in diabetic patients following various stress phenomena. In studying these cases, a latent time interval between the stress phenomena and the onset of neuropathy was noted; the significance of this will be indicated.

The following cases are reported as examples of the relationship of the neuropathy to various stresses.

Case Reports. CASE 1. This 62-year-old white woman was first admitted to the Mount Sinai Hospital because of congestive heart failure. She was a known diabetic for the past 13 years, having been under satisfactory control with minimal glycosuria and no shock. She had recently been taking 25 units of isophane insulin daily.

On examination, in addition to signs of congestive heart failure, diabetic retinopathy and diabetic neuropathy were present. The latter was manifested by absence of all deep reflexes and vibratory sense in the lower extremities. Laboratory examination: urine was negative except for an occasional white blood cell; hemoglobin 13.8 gm.%; white blood count normal; sedimentation rate, blood urea nitrogen, chloride, total protein, sodium and potassium were all normal. Blood sugar ranged from 71 to 102 mg. per 100 ml.

The patient responded well to energetic treatment for the heart failure. Following discharge she maintained relatively good health for 6 months. There then developed an ulceration of the left heel associated with considerable pain for which she was readmitted. There was a gangrenous ulcer of the left heel and an associated acute left saphenous vein thrombophlebitis. Peripheral pulses were absent in the lower extremities. The neurological status was unchanged. There were no evidences of congestive heart failure.

Laboratory findings were essentially as on the first admission with no significant abnormalities. In particular, the urine was completely negative, including microscopic analysis.

Because of spreading infection and gangrene, a below the knee amputation was performed. Postoperative course was uneventful until 10 days later when she complained of an inability to void. At first she was able to void following the administration of urecholine, but this drug soon lost its effect as the condition advanced. By the fifteenth postoperative day she had to be catheterized consistently, with the average amount of urine obtained being 800 ml. During this period of time, the urine, which had been negative, became markedly infected and contained many white cells with clumps. Cystometric examination revealed a markedly hypotonic bladder with slight desire present at 350 ml. and pain not developing until 750 ml. at 25 mm. of water pressure had been introduced. Attempted control with an indwelling Foley catheter was unsuccessful. Tidal drainage also failed to alleviate the urinary retention. Reevaluation of the status at this time revealed that she had been losing weight progressively because of anorexia and marked depression; the diabetic status was under excellent control. The neurological examination now revealed absent deep reflexes in all extremities, paresis of the thigh muscles, and atrophy of the small muscles of the hands and the muscles of the lower extremities. After the urologists had exhausted all their nonoperative attempts at treating the neurogenic bladder, a transurethral resection of the internal vesical sphincter was performed. Within 6 days the patient was voiding well without a catheter and in 10 days the residual urine was only 30 ml. Her weight, appetite, mood and general demeanor improved dramatically following the re-establishment of proper bladder emptying. The amputation wound healed and the patient was able to be satisfactorily fitted with a prosthesis.

COMMENT. Here, the neurogenic bladder followed amputation. The latent interval from operation to urinary retention was 10 days. It is important again to emphasize that at no time was her diabetes in poor control. The dramatic response to resection of the internal vesical sphincter, which is the specific therapy for this condition, is worthy of note.

CASE 2. This 63-year-old white man was admitted to the Mount Sinai Hospital because of inability to walk. One year ago a transurethral resection of the prostate was performed for symptoms of urinary obstruction; intravenous Pentothal sodium was employed for anesthesia. Prior to operation, the patient had no symptoms or signs pertaining to the locomotor system. Two weeks after operation, he noted weakness in the legs, particularly on walking. One month after operation the weakness became markedly accentuated with his knees buckling under him. This progressed so that 6 months later he was unable to walk at all. Associated with this were marked constipation and almost continuous dribbling of urine. Past history is significant in that two and a half years ago an elevated blood sugar was noted which was unaccompanied by glycosuria. Repeated urinalysis since then had revealed infrequent traces of glycosuria.

Physical examination: the blood pressure was 180/80 mm. Hg; fundi were normal; peripheral pulses were normal. Neurological examination revealed definite weakness of both lower extremities, more marked proximally, with atrophy of the thigh and calf muscles; the knee jerks and ankle jerks were absent; there was impairment of vibratory sense in both lower extremities and some impairment of light touch.

Laboratory examination: blood count normal; urine entirely normal; fasting blood sugar 135 mg. per 100 ml.; blood urea nitrogen, total protein, albumin-globulin ratio, calcium, phosphorus, alkaline and acid phosphatase all normal. Glucose tolerance test revealed a diabetic type of curve with a 2-hour value of 284 mg. per 100 ml. Lumbar puncture on two occasions revealed clear colorless fluid without cells, negative serologic reaction, normal manometric readings and total proteins of 108 and 112 mg. per 100 ml. Sweating test disclosed diminution in sweating response over the feet, ankles, and calves. Myelogram, intravenous pyelogram and cystogram were normal; roentgenographic examination of the lumbosacral spine was negative except for hypertrophic spurring.

The patient's diabetes was well controlled by diet alone. Cystoscopy revealed a defect of the external sphincter which accounted for the patient's urinary incontinence. The patient was discharged for chronic care.

COMMENT. This is an instance of neuropathy in a diabetic commencing 2 weeks after prostate surgery. Sig-

nificantly, the patient's diabetes was well controlled before, during and after operation. It is important to note that he did not have spinal anesthesia.

CASE 3. This was the first Mount Sinai Hospital admission of a 52-year-old white man. Ten months ago he experienced signs of congestive heart failure which responded to treatment with digitalis and Mercuhydrin. During this period, he noted fatigability and anorexia. Four days before admission, he developed a severe infection with marked exacerbation of a chronic cough, now productive of large amounts of yellowish sputum.

Past history included the fact that glycosuria had been noted 15 years ago. He had never taken insulin, though he had followed a diet restricted in carbohydrates. Frequent routine testing of urine at home had yielded consistently negative results. Impotence had been present for the past 2 years. Family history included the fact that one brother had both diabetes and heart disease.

On examination, he was acutely ill with temperatures to 104.5° and respirations of 36 per minute. There were many capillary aneurysms and waxy exudates in the fundi; the lungs showed diffusely scattered respiratory rales and expiratory wheezes; the deep tendon reflexes were absent in the lower extremities and sensation to pin prick was diminished; there was pitting edema of the feet extending up to the knees.

Laboratory investigation showed: hemoglobin 14 gm.%; leukocytosis of 13,000 per c.mm. with a 93% polymorphonuclear count; the urine contained a trace of albumin and occasional glycosuria; blood sugar 147 mg. per 100 ml.; the carbon dioxide-combining power, chloride, sodium, potassium, cholesterol, urea nitrogen and alkaline phosphatase were all within normal limits; the total protein was 7.6 gm.% with albumin 3.6 and globulin 4.0; sedimentation rate 93 mm. per hour; influenza H.A.I. was positive for Far Eastern influenza. Roentgenographic examination of the chest showed increase in prominence of the pulmonary markings at the right base and enlargement of the heart towards the left; intravenous pyelogram was normal; examination of the lumbosacral spine, aside from mild osteo-arthritic changes, was normal. Bone marrow aspiration was normal.

It was evident that the patient was suffering from chronic bronchitis and emphysema with superimposed severe infection of Far Eastern influenza, and congestive heart failure. Treatment consisted of antibiotics and an appropriate cardiac regimen. The temperature was elevated to 104.5° each day for the first 3 days and then fell by lysis. The diabetes presented no problem and insulin was not necessary; the urine showed only occasional glycosuria in small amounts.

Fourteen days after onset, at which time the pulmonary infection and heart failure had cleared, he complained of lancinating pain in the lower extremities. This became increasingly severe, especially at night, keeping him from sleep. He also noted progressive weakness and atrophy of all four extremities, particularly the lower. Neurological examination now revealed that both pupils reacted to light and in accommodation; there was moderate weakness of the upper extremities; partial atrophy of the thenar and hypothenar eminences as well as of the web spaces of the hands was present; there was marked atrophy of the quadriceps bilaterally; knee jerks, ankle jerks, radial and biceps reflexes were absent, while the triceps were markedly diminished; vibratory sensation was decreased in the upper and lower extremities; pin prick and touch were diminished below the knees. The peripheral pulses were palpable. Lumbar puncture revealed clear, colorless fluid with normal manometric studies, negative serologic and collodial gold reactions, absence of cells but an increase of the spinal fluid protein to 101 mg. per 100 ml. This picture was compatible with diabetic myeloradiculoneuropathy.

Shortly after developing the neuritic symptoms, he began to spill larger amounts of sugar, so that insulin administration became necessary. Five weeks later, he complained of feeling dizzy and light-headed on arising. Investigation determined that he now had an orthostatic hypotension. Blood pressure in the prone position was 160/85 mm. Hg and on standing dropped precipitously to 70/50 mm. Hg. One other fact of interest is worthy of mention; namely, that throughout his entire hospital stay, including the period during which he no longer was febrile, he had a persistent tachycardia. Hyperthyroidism was ruled out by appropriate investigation. It is inferred that the tachycardia was a manifestation of his neuropathy.

COMMENT This case is an example of severe exacerbation of a relatively asymptomatic diabetic neuropathy brought about by an acute infectious episode. The neuropathy, which had a latent period of 14 days, was

manifested by the extremity pains with nocturnal exacerbation, the muscular atrophy and paresis and later the orthostatic hypotension, the tachycardia, and elevated spinal fluid protein. He had been under good control prior to the onset of the present neurological picture.

CASE 4. This 57-year-old white woman sustained her second myocardial infarction and was admitted to the Mount Sinai Hospital. Her diabetes which was of 6 years' duration, had always been under good control. On admission, the evidences of acute coronary artery occlusion were present and comprised severe precordial pain, a fall in blood pressure, fever, leukocytosis, increase in sedimentation rate and transaminase, and electrocardiographic changes indicative of anterior-wall infarction. The neurological examination was normal. The course was essentially uneventful with no evidences of congestive heart failure; diabetic control was excellent. On the twentieth day after infarction, the patient began to complain of burning pain in both lower extremities, particularly in the region of the calves. The pain persisted and gradually became worse. In view of the location of the pain in a patient with known myocardial infarction, a tentative diagnosis of thrombophlebitis was made. However, the absence of signs of inflammation, swelling and fever led to further investigation. This revealed neurological changes consisting of tenderness throughout both calves, unrelated to venous distribution, markedly depressed knee jerks (which had hitherto been active), absent ankle jerks, and absent vibratory sensation from the hips down. Further historical evaluation indicated that the pain was intensified at night and relieved during the day. When the patient became ambulatory, she noted that walking improved the symptoms.

COMMENT. This diabetic patient developed a neuropathy 21 days after an acute myocardial infarction while under good diabetic control. Of incidental interest is the simulation of thrombophlebitis.

CASE 5. This 62-year-old white man had known diabetes of 8 years' duration. He had been treated chiefly with dietary control on which regimen his urine remained sugar-free. He was seen for a routine check-up at which time the urine was sugar-free. Complete neurological examination was done, because he had injured his head on the morning of the examination, and was found to be normal.

The patient was a known depressive and had been quite depressed for some time. That afternoon he took an overdose of barbiturates (Nembutal). He was admitted to the Mount Sinai Hospital in deep coma; there was flaccidity with complete areflexia. The diagnosis of barbiturate poisoning was proven by chemical examination of gastric contents, urine and spinal fluid. He remained in coma for 3 days. On regaining consciousness the reflexes slowly returned. On the sixth day, he began to complain of severe paresthesias involving primarily the lower extremities, plus shooting pains radiating from the hip down the posterior aspect of both lower extremities in sciatic distribution, the left greater than the right. The pains were exaggerated in the late afternoon but were even worse at night, frequently awakening him from sleep. The paresthesias were accompanied by sensations of coldness and numbness in the feet. Examination revealed diminished vibratory sensation, diminished touch and pin prick in both lower extremities below the knees. Lumbar puncture revealed a spinal fluid protein of 64 mg. per 100 ml.

COMMENT. The neuropathy appeared 6 days after the barbiturate coma. It is significant that he never had any of these symptoms prior to the onset of coma and that the diabetes had been under good control. Under observation, these symptoms improved, so that 5 months later they had almost, but not entirely, cleared.

CASE 6. This 64-year-old white man was admitted because of progressively severe dyspnea, anorexia and cough. The family history revealed that his mother had diabetes. For the past 6 months there had been anorexia, nausea, insomnia, paresthesias of the feet and a 30-pound weight loss. There was no history of diabetes, polyuria, or polydypsia.

On examination, he was markedly tachypneic and cyanotic with evidence of congestive heart failure. Vibratory sensation was decreased below the knees bilaterally, the remainder of the neurological examination was negative. No hemorrhages or exudates were visualized in the fundi. Blood pressure was 115/85 mm. Hg.

Laboratory examination revealed a 3 plus

glycosuria without acetonuria and 2 plus albuminuria; blood count was negative except for a moderate leukocytosis; blood analyses showed a fasting blood sugar of 304 mg. per 100 ml.; total protein 7.2 gm.%, albumin 3, globulin 4.2; blood cholesterol, urea nitrogen, alkaline and acid phosphatase, chloride, sodium and potassium were all normal; CO_2-combining power elevated to 60 volumes %. Roentgenographic examination of the chest showed diffuse linear and nodular infiltrations throughout both lung fields.

The diabetes, which had not been recognized prior to admission, was readily controlled on 20 units of NPH insulin daily. Intensive investigation of the cardiac and pulmonary status resulted in a diagnosis of idiopathic pulmonary fibrosis. In view of this, the patient received a course of cortisone 5 weeks after insulin had been started. The insulin requirement subsequently rose to 30 units. Three weeks after starting cortisone, the patient noted the development of a "slapping" gait to which little attention was paid, and with which he was discharged.

Following discharge from the hospital, the "slapping" gait became progressively more severe. Weakness in both extremities became so extreme that he was unable to walk without assistance. Six months later he experienced a sensation of coldness in the lower extremities extending up to the knees, and in the upper extremities extending half way up the forearm, accompanied by tingling. Because of persistent weakness he was readmitted to the hospital. In the interim his diabetes had been well controlled.

Examination revealed marked improvement in his pulmonary status. Pupils were normal; fundi were negative. Neurological examination revealed atrophy of the interossei, thenar and hypothenar muscles of the hands, marked atrophy and weakness of the quadriceps and the dorsi-flexors of the lower extremities, left greater than the right; the knee jerks and ankle jerks were bilaterally absent; he walked with a "slapping" gait.

Urinalysis was negative; fasting blood sugar was 124 mg. per 100 ml.; all other analyses were normal. Lumbar puncture revealed clear fluid under normal pressure without any evidence of block; total spinal fluid protein was 66 mg. per 100 ml. The corticosteroids were stopped and physiotherapy was instituted. Under this regimen the patient showed signs of improvement. Prior to discharge, his diabetes was well controlled on diet alone without insulin.

COMMENT. This patient represents an instance of diabetic neuropathy following the institution of cortisone treatment. The initial manifestation began after 3 weeks of therapy and progressed for fully six months. During this time the diabetes remained under good control. At the time of his second admission, the cortisone was stopped and coincidentally his neurological manifestations started to improve. Of added interest is the fact that paresthesias and impaired vibratory sensation were present at least 6 months before diabetes was diagnosed and were unaccompanied by any symptoms of uncontrolled glycosuria. The obvious parallel between a stress situation and corticosteroid administration is suggested.

CASE 7. This 62-year-old man was admitted with a chief complaint of bilateral lower extremity pain of 8 months' duration. Nine months ago he sustained a cerebral vascular accident manifested by loss of consciousness, aphasia and right-sided paresis. There was a gradual return of muscle function and speech. One month later he developed pain in the thighs, calves and feet occurring chiefly at night, severe enough to prevent sleep and relieved by walking. During this time he had moderate anorexia accompanied by a 35-pound weight loss without polyuria or polydypsia.

Physical examination showed blood pressure of 170/80 mm. Hg; heart and lungs were normal; the liver was palpable two finger breadths below the costal margin; the peripheral pulses were palpable; there was no evidence of diabetic retinopathy. Neurologically, there was a mild expressive aphasia; the reflexes in the lower extremities were absent; vibratory sensation was absent below the iliac crest; there were no Babinski signs. Lumbar puncture was entirely negative except for an elevation of spinal fluid protein to 62 mg. per 100 ml.; intravenous pyelogram, skull roentgenograms and films of the lumbosacral spine were all negative. Because of the suggestive neurological syndrome, investigation for the presence of diabetes was made and the diagnosis of diabetes was established.

COMMENT. In this case the manifestation of diabetic neuropathy occurred

one month after a cerebral vascular accident. It is of further interest that the neuropathy was the initial clinical manifestation of the diabetes. Follow-up examination indicated disappearance of the symptoms.

CASE 8. This 57-year-old white woman entered the hospital because of progressive weakness in the lower extremities. Diabetes mellitus was diagnosed 5 years ago following the onset of polydypsia and polyuria. This had been controlled with diet alone until 6 months ago when the symptoms increased and the patient also developed pruritus vulvae. She was given isophane insulin, 40 units daily, which served to bring the diabetes under excellent control. Four weeks after insulin was started, she noticed weakness in both lower extremities. This increased progressively, so that she developed difficulty in walking, easy fatigability, difficulty in arising from a chair and climbing stairs. Not long after, she became unsteady and fell on several occasions when her knees gave way. The paresthesias in her legs and feet also increased, but to a lesser degree. Along with these symptoms, she manifested a significant depression and marked anxiety. Family history was negative except for the presence of diabetes in several of her cousins.

Physical examination: the heart was not enlarged; the liver was not palpable; pelvic examination was negative; the peripheral pulses were patent. The neurological examination showed the cranial nerves to be entirely normal; there was no diabetic retinopathy. The abnormal findings were confined to the lower extremities. Here there was distinct and marked weakness of both hips with difficulty in getting out of a chair; there was marked weakness of flexion at the knees; the thigh and calf muscles were severely atrophied bilaterally; knee jerks and ankle jerks were absent but no pathological reflexes were obtained; vibratory sense was impaired below both iliac crests, and there was some loss of position sense of the toes.

Laboratory examination: hemoglobin 13.2 gm.%; blood count normal; urinalysis negative; blood urea nitrogen, calcium, phosphorus, total protein, cholesterol, alkaline phosphatase and carbon-dioxide-combining power were all normal; gastric analysis showed the presence of free hydrochloric acid. Roentgenographic examinations of the chest and of the spine were normal; absorption of radioactive iodine was normal; spinal fluid was clear and contained no cells; the total protein was elevated to 102 mg. per 100 ml. Blood and spinal fluid Wassermann tests were negative.

Shortly after admission, and while insulin administration was continued, the patient began to improve spontaneously. This continued to progress rapidly to resolution.

COMMENT. The neuropathy occurred 28 days after starting control of the diabetes with insulin and while there was good control. Insulin *per se* has been exonerated as a causative factor (Ellenberg[3]). The supposition is that the relatively sudden change of the homeostasis produces the equivalent of a stress situation.

CASE 9. This was the first Mount Sinai Hospital admission of a 47-year-old white woman complaining of pain in the right arm-pit, right upper chest and left lower extremity. The patient's diabetes was discovered 5 years ago. Since then she had tested her urine about once a month, always detecting glycosuria but never having it treated. Six months prior to admission, in the course of a medical examination, glycosuria was again noted and hyperglycemia (288 mg. per 100 ml.) was documented. In view of the long-standing untreated diabetes, and persistent weight loss, specific therapy in the form of tolbutamide was instituted. The patient received 1 gm. a day. Fourteen days later she experienced the sudden onset of severe burning pain in the right scapula area radiating into the right axilla and the right breast. Two weeks after this, she noted tingling pain and paresthesia beginning in the left buttock which radiated down the lateral aspect of the left lower extremity to the mid-thigh. The pains were persistent, severe, always worse at night and relieved only by large amounts of narcotics, salicylates, and tranquilizers in combination. There was progressive weakness of both lower extremities, the left greater than the right, with an accompanying sensation of numbness. In association with these symptoms, the patient became very depressed and developed anorexia. Because of the persistence of symptoms and their coincidental association with the administration of tolbutamide, the drug was discontinued after 4 months. Nevertheless, the symptoms continued unabated.

Past history included total hysterectomy at age 23 for fibroid tumors. The family history revealed the presence of diabetes in her

nificantly, the patient's diabetes was well controlled before, during and after operation. It is important to note that he did not have spinal anesthesia.

CASE 3. This was the first Mount Sinai Hospital admission of a 52-year-old white man. Ten months ago he experienced signs of congestive heart failure which responded to treatment with digitalis and Mercuhydrin. During this period, he noted fatigability and anorexia. Four days before admission, he developed a severe infection with marked exacerbation of a chronic cough, now productive of large amounts of yellowish sputum.

Past history included the fact that glycosuria had been noted 15 years ago. He had never taken insulin, though he had followed a diet restricted in carbohydrates. Frequent routine testing of urine at home had yielded consistently negative results. Impotence had been present for the past 2 years. Family history included the fact that one brother had both diabetes and heart disease.

On examination, he was acutely ill with temperatures to 104.5° and respirations of 36 per minute. There were many capillary aneurysms and waxy exudates in the fundi; the lungs showed diffusely scattered respiratory rales and expiratory wheezes; the deep tendon reflexes were absent in the lower extremities and sensation to pin prick was diminished; there was pitting edema of the feet extending up to the knees.

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Fourteen days after onset, at which time the pulmonary infection and heart failure had cleared, he complained of lancinating pain in the lower extremities. This became increasingly severe, especially at night, keeping him from sleep. He also noted progressive weakness and atrophy of all four extremities, particularly the lower. Neurological examination now revealed that both pupils reacted to light and in accommodation; there was moderate weakness of the upper extremities; partial atrophy of the thenar and hypothenar eminences as well as of the web spaces of the hands was present; there was marked atrophy of the quadriceps bilaterally; knee jerks, ankle jerks, radial and biceps reflexes were absent, while the triceps were markedly diminished; vibratory sensation was decreased in the upper and lower extremities; pin prick and touch were diminished below the knees. The peripheral pulses were palpable. Lumbar puncture revealed clear, colorless fluid with normal manometric studies, negative serologic and collodial gold reactions, absence of cells but an increase of the spinal fluid protein to 101 mg. per 100 ml. This picture was compatible with diabetic myeloradiculoneuropathy.

Shortly after developing the neuritic symptoms, he began to spill larger amounts of sugar, so that insulin administration became necessary. Five weeks later, he complained of feeling dizzy and light-headed on arising. Investigation determined that he now had an orthostatic hypotension. Blood pressure in the prone position was 160/85 mm. Hg and on standing dropped precipitously to 70/50 mm. Hg. One other fact of interest is worthy of mention; namely, that throughout his entire hospital stay, including the period during which he no longer was febrile, he had a persistent tachycardia. Hyperthyroidism was ruled out by appropriate investigation. It is inferred that the tachycardia was a manifestation of his neuropathy.

COMMENT This case is an example of severe exacerbation of a relatively asymptomatic diabetic neuropathy brought about by an acute infectious episode. The neuropathy, which had a latent period of 14 days, was

manifested by the extremity pains with nocturnal exacerbation, the muscular atrophy and paresis and later the orthostatic hypotension, the tachycardia, and elevated spinal fluid protein. He had been under good control prior to the onset of the present neurological picture.

CASE 4. This 57-year-old white woman sustained her second myocardial infarction and was admitted to the Mount Sinai Hospital. Her diabetes which was of 6 years' duration, had always been under good control. On admission, the evidences of acute coronary artery occlusion were present and comprised severe precordial pain, a fall in blood pressure, fever, leukocytosis, increase in sedimentation rate and transaminase, and electrocardiographic changes indicative of anterior-wall infarction. The neurological examination was normal. The course was essentially uneventful with no evidences of congestive heart failure; diabetic control was excellent. On the twentieth day after infarction, the patient began to complain of burning pain in both lower extremities, particularly in the region of the calves. The pain persisted and gradually became worse. In view of the location of the pain in a patient with known myocardial infarction, a tentative diagnosis of thrombophlebitis was made. However, the absence of signs of inflammation, swelling and fever led to further investigation. This revealed neurological changes consisting of tenderness throughout both calves, unrelated to venous distribution, markedly depressed knee jerks (which had hitherto been active), absent ankle jerks, and absent vibratory sensation from the hips down. Further historical evaluation indicated that the pain was intensified at night and relieved during the day. When the patient became ambulatory, she noted that walking improved the symptoms.

COMMENT. This diabetic patient developed a neuropathy 21 days after an acute myocardial infarction while under good diabetic control. Of incidental interest is the simulation of thrombophlebitis.

CASE 5. This 62-year-old white man had known diabetes of 8 years' duration. He had been treated chiefly with dietary control on which regimen his urine remained sugar-free. He was seen for a routine check-up at which time the urine was sugar-free. Complete neurological examination was done, because he had injured his head on the morning of the examination, and was found to be normal.

The patient was a known depressive and had been quite depressed for some time. That afternoon he took an overdose of barbiturates (Nembutal). He was admitted to the Mount Sinai Hospital in deep coma; there was flaccidity with complete areflexia. The diagnosis of barbiturate poisoning was proven by chemical examination of gastric contents, urine and spinal fluid. He remained in coma for 3 days. On regaining consciousness the reflexes slowly returned. On the sixth day, he began to complain of severe paresthesias involving primarily the lower extremities, plus shooting pains radiating from the hip down the posterior aspect of both lower extremities in sciatic distribution, the left greater than the right. The pains were exaggerated in the late afternoon but were even worse at night, frequently awakening him from sleep. The paresthesias were accompanied by sensations of coldness and numbness in the feet. Examination revealed diminished vibratory sensation, diminished touch and pin prick in both lower extremities below the knees. Lumbar puncture revealed a spinal fluid protein of 64 mg. per 100 ml.

COMMENT. The neuropathy appeared 6 days after the barbiturate coma. It is significant that he never had any of these symptoms prior to the onset of coma and that the diabetes had been under good control. Under observation, these symptoms improved, so that 5 months later they had almost, but not entirely, cleared.

CASE 6. This 64-year-old white man was admitted because of progressively severe dyspnea, anorexia and cough. The family history revealed that his mother had diabetes. For the past 6 months there had been anorexia, nausea, insomnia, paresthesias of the feet and a 30-pound weight loss. There was no history of diabetes, polyuria, or polydypsia.

On examination, he was markedly tachypneic and cyanotic with evidence of congestive heart failure. Vibratory sensation was decreased below the knees bilaterally, the remainder of the neurological examination was negative. No hemorrhages or exudates were visualized in the fundi. Blood pressure was 115/85 mm. Hg.

Laboratory examination revealed a 3 plus

glycosuria without acetonuria and 2 plus albuminuria; blood count was negative except for a moderate leukocytosis; blood analyses showed a fasting blood sugar of 304 mg. per 100 ml.; total protein 7.2 gm.%, albumin 3, globulin 4.2; blood cholesterol, urea nitrogen, alkaline and acid phosphatase, chloride, sodium and potassium were all normal; CO_2-combining power elevated to 60 volumes %. Roentgenographic examination of the chest showed diffuse linear and nodular infiltrations throughout both lung fields.

The diabetes, which had not been recognized prior to admission, was readily controlled on 20 units of NPH insulin daily. Intensive investigation of the cardiac and pulmonary status resulted in a diagnosis of idiopathic pulmonary fibrosis. In view of this, the patient received a course of cortisone 5 weeks after insulin had been started. The insulin requirement subsequently rose to 30 units. Three weeks after starting cortisone, the patient noted the development of a "slapping" gait to which little attention was paid, and with which he was discharged.

Following discharge from the hospital, the "slapping" gait became progressively more severe. Weakness in both extremities became so extreme that he was unable to walk without assistance. Six months later he experienced a sensation of coldness in the lower extremities extending up to the knees, and in the upper extremities extending half way up the forearm, accompanied by tingling. Because of persistent weakness he was readmitted to the hospital. In the interim his diabetes had been well controlled.

Examination revealed marked improvement in his pulmonary status. Pupils were normal; fundi were negative. Neurological examination revealed atrophy of the interossei, thenar and hypothenar muscles of the hands, marked atrophy and weakness of the quadriceps and the dorsi-flexors of the lower extremities, left greater than the right; the knee jerks and ankle jerks were bilaterally absent; he walked with a "slapping" gait.

Urinalysis was negative; fasting blood sugar was 124 mg. per 100 ml.; all other analyses were normal. Lumbar puncture revealed clear fluid under normal pressure without any evidence of block; total spinal fluid protein was 66 mg. per 100 ml. The corticosteroids were stopped and physiotherapy was instituted. Under this regimen the patient showed signs of improvement. Prior to discharge, his diabetes was well controlled on diet alone without insulin.

COMMENT. This patient represents an instance of diabetic neuropathy following the institution of cortisone treatment. The initial manifestation began after 3 weeks of therapy and progressed for fully six months. During this time the diabetes remained under good control. At the time of his second admission, the cortisone was stopped and coincidentally his neurological manifestations started to improve. Of added interest is the fact that paresthesias and impaired vibratory sensation were present at least 6 months before diabetes was diagnosed and were unaccompanied by any symptoms of uncontrolled glycosuria. The obvious parallel between a stress situation and corticosteroid administration is suggested.

CASE 7. This 62-year-old man was admitted with a chief complaint of bilateral lower extremity pain of 8 months' duration. Nine months ago he sustained a cerebral vascular accident manifested by loss of consciousness, aphasia and right-sided paresis. There was a gradual return of muscle function and speech. One month later he developed pain in the thighs, calves and feet occurring chiefly at night, severe enough to prevent sleep and relieved by walking. During this time he had moderate anorexia accompanied by a 35-pound weight loss without polyuria or polydypsia.

Physical examination showed blood pressure of 170/80 mm. Hg; heart and lungs were normal; the liver was palpable two finger breadths below the costal margin; the peripheral pulses were palpable; there was no evidence of diabetic retinopathy. Neurologically, there was a mild expressive aphasia; the reflexes in the lower extremities were absent; vibratory sensation was absent below the iliac crest; there were no Babinski signs. Lumbar puncture was entirely negative except for an elevation of spinal fluid protein to 62 mg. per 100 ml.; intravenous pyelogram, skull roentgenograms and films of the lumbosacral spine were all negative. Because of the suggestive neurological syndrome, investigation for the presence of diabetes was made and the diagnosis of diabetes was established.

COMMENT. In this case the manifestation of diabetic neuropathy occurred

one month after a cerebral vascular accident. It is of further interest that the neuropathy was the initial clinical manifestation of the diabetes. Follow-up examination indicated disappearance of the symptoms.

CASE 8. This 57-year-old white woman entered the hospital because of progressive weakness in the lower extremities. Diabetes mellitus was diagnosed 5 years ago following the onset of polydypsia and polyuria. This had been controlled with diet alone until 6 months ago when the symptoms increased and the patient also developed pruritus vulvae. She was given isophane insulin, 40 units daily, which served to bring the diabetes under excellent control. Four weeks after insulin was started, she noticed weakness in both lower extremities. This increased progressively, so that she developed difficulty in walking, easy fatigability, difficulty in arising from a chair and climbing stairs. Not long after, she became unsteady and fell on several occasions when her knees gave way. The paresthesias in her legs and feet also increased, but to a lesser degree. Along with these symptoms, she manifested a significant depression and marked anxiety. Family history was negative except for the presence of diabetes in several of her cousins.

Physical examination: the heart was not enlarged; the liver was not palpable; pelvic examination was negative; the peripheral pulses were patent. The neurological examination showed the cranial nerves to be entirely normal; there was no diabetic retinopathy. The abnormal findings were confined to the lower extremities. Here there was distinct and marked weakness of both hips with difficulty in getting out of a chair; there was marked weakness of flexion at the knees; the thigh and calf muscles were severely atrophied bilaterally; knee jerks and ankle jerks were absent but no pathological reflexes were obtained; vibratory sense was impaired below both iliac crests, and there was some loss of position sense of the toes.

Laboratory examination: hemoglobin 13.2 gm.%; blood count normal; urinalysis negative; blood urea nitrogen, calcium, phosphorus, total protein, cholesterol, alkaline phosphatase and carbon-dioxide-combining power were all normal; gastric analysis showed the presence of free hydrochloric acid. Roentgenographic examinations of the chest and of the spine were normal; absorption of radioactive iodine was normal; spinal fluid was clear and contained no cells; the total protein was elevated to 102 mg. per 100 ml. Blood and spinal fluid Wassermann tests were negative.

Shortly after admission, and while insulin administration was continued, the patient began to improve spontaneously. This continued to progress rapidly to resolution.

COMMENT. The neuropathy occurred 28 days after starting control of the diabetes with insulin and while there was good control. Insulin *per se* has been exonerated as a causative factor (Ellenberg[3]). The supposition is that the relatively sudden change of the homeostasis produces the equivalent of a stress situation.

CASE 9. This was the first Mount Sinai Hospital admission of a 47-year-old white woman complaining of pain in the right arm-pit, right upper chest and left lower extremity. The patient's diabetes was discovered 5 years ago. Since then she had tested her urine about once a month, always detecting glycosuria but never having it treated. Six months prior to admission, in the course of a medical examination, glycosuria was again noted and hyperglycemia (288 mg. per 100 ml.) was documented. In view of the long-standing untreated diabetes, and persistent weight loss, specific therapy in the form of tolbutamide was instituted. The patient received 1 gm. a day. Fourteen days later she experienced the sudden onset of severe burning pain in the right scapula area radiating into the right axilla and the right breast. Two weeks after this, she noted tingling pain and paresthesia beginning in the left buttock which radiated down the lateral aspect of the left lower extremity to the mid-thigh. The pains were persistent, severe, always worse at night and relieved only by large amounts of narcotics, salicylates, and tranquilizers in combination. There was progressive weakness of both lower extremities, the left greater than the right, with an accompanying sensation of numbness. In association with these symptoms, the patient became very depressed and developed anorexia. Because of the persistence of symptoms and their coincidental association with the administration of tolbutamide, the drug was discontinued after 4 months. Nevertheless, the symptoms continued unabated.

Past history included total hysterectomy at age 23 for fibroid tumors. The family history revealed the presence of diabetes in her

mother, father and two paternal aunts, one of whom had an amputation of an extremity for diabetic gangrene.

Physical examination revealed a middle aged white woman complaining of pain. Weight loss was evident. Fundi revealed diabetic retinopathy. Heart and lungs were normal; blood pressure 130/80 mm. Hg; liver palpable one finger breadth below the costal margin. Neurological examination revealed slow cautious gait; difficulty in arising from a squatting position; weakness of flexion at the hips and both knees; absent knee jerks and ankle jerks; hyperalgesia over the right upper thoracic segments T_7 to T_{10} and on the left between S_1 to S_3; there was decreased vibratory sensation over all the toes. The pupils were unequal, irregular and reacted poorly to light.

Laboratory investigation revealed a normal blood count; trace of albumin in the urine, glycosuria one to four plus; blood urea nitrogen 13 mg. per 100 ml.; cholesterol 345 mg. per 100 ml.; blood Wassermann negative; fasting blood sugar 230 mg. per 100 ml. Roentgenographic examination of the chest and dorso-lumbosacral spine was normal. Lumbar puncture revealed clear fluid under normal pressure with normal manometric reading, cell count, Wassermann and colloidal gold; the total protein was elevated to 90 mg. per 100 ml.

In view of the uncontrolled diabetes, the patient was started on tolbutamide, 2 gm. per day. This dose was soon reduced to 1 gm. a day and has been maintained uninterruptedly since. While in the hospital her symptoms started to abate and have progressively improved.

COMMENT. The neuropathy began 14 days after institution of diabetic control with tolbutamide and while good control existed. Tolbutamide has been absolved as the noxious agent but merely acts as the medium for control of the diabetes (Ellenberg[4]). The homeostatic changes thereby resulting then produce the effects of a stress mechanism.

Discussion. It seems apparent from the cases herein reported that neuropathy in diabetes may follow a period of stress independent of the state of diabetic control. The stress factors involved in this series include amputation, prostatic and abdominal surgery, infection, coronary thrombosis, cerebral vascular accident, corticosteroid therapy, barbiturate coma, and the institution of control of the diabetes by insulin or tolbutamide. Additional stress factors mentioned in the literature include trauma, hyperthyroidism, and diabetic coma. The variability of the factors all yielding a similar result indicates a common final pathway. It also suggests the possibility of common pathogenetic mechanisms, but this remains a matter of conjecture.

The objection may be raised that the neuropathy could be due to incidentally activated quiescent, neurotropic viruses unrelated to diabetes. However, the location of the clinical findings are hardly capricious as one would expect under these circumstances. On the contrary, they follow in all detail the symptoms, signs, spinal fluid findings and course characteristic of the recognized forms of diabetic neuropathy. It should be pointed out that the neuropathy does not necessarily appear *de novo;* actually, several of our patients had preceding objective evidences of diabetic neuropathy which was essentially asymptomatic. The stress probably serves to precipitate the neurological syndrome into the symptomatic clinical horizon in those diabetics who either have a relatively asymptomatic neuopathy or have the potential components for the development of this complication.

An observation that has heretofore escaped documentation is the fact that there is a fairly uniform time interval between the stress factor and the onset of the neuropathy. As shown in Table 1, the time interval varied from 7 to 30 days with an average of 18½ days. This fact assumes even greater significance in the light of a parallel latent period existing in many other situations wherein neuropathy follows a known

inciting factor. For example, post-inoculation neuropathy has a latent period of 7 to 14 days (Miller and Stanton[14]); a case of neuropathy followed vaccination by 25 days (Young and Moore[20]); peripheral neuritis due to penicillin developed in 7 cases between 10 to 21 days, with an average of 15 days (Kolb and Gray[12]); the latent period of neuritis following abortifacients, typified by apiol, has a latent period of 14 to 21 days (King[11]); and neuritis following arsenical therapy occurs 14 to 21 days later (Hyman *et al.*[8]). It is of further interest that toxic manifestations of drugs where the toxicity is manifested not by neuropathy but by intrahepatic cholestasis, such as following arsphenamine (Hanger and Gutman[7]), thiouracil (Gargill and Lesses[5]), chlorpromazine (Werther and Korelitz[19]) and chlorpropamide (Unpublished observation[18]) have a similar stereotyped range of latent period. This time interval also calls to mind the setting in the development of acute glomerulonephritis and acute rheumatism.

TABLE 1.—TABLE SHOWING THE LATENT INTERVAL OF ONSET OF NEUROPATHY FOLLOWING VARIOUS STRESSES IN 20 PATIENTS

Stress Factor	*Time Interval*
Surgery:—prostate	24 days
" "	20 "
" amputation	10 "
" abdominal	10 "
Infection	14 "
"	21 "
Myocardial infarction	20 "
" "	24 "
Barbiturate coma	7 "
Corticosteroid therapy	23 "
Cerebral vascular accident	30 "
Control with insulin	7 "
" " "	28 "
" " "	14 "
" " "	20 "
" " "	21 "
" " "	15 "
Control with tolbutamide	12 "
" " "	21 "
" " "	28 "
Average	18.5 days

The presence of a latent period strengthens the validity of the contention that the stress factors are related to the onset of neuropathy and are not a purely coincidental association. The time interval also raises the possibility of the presence of an operative toxic or metabolic factor in these situations; this, however, remains pure conjecture. The fact that the comparable situations with known toxic factors act in the same way and express themselves similarly would seem to support such an hypothesis.

From the clinical point of view, it is important that the physician be aware of this entity so that proper diagnostic recognition will ensue and appropriate measures be instituted.

Summary. In this paper, another factor unrelated to diabetic control, namely stress, has been shown to be a determinant in the development of diabetic neuropathy. The stress factors enumerated and exemplified include amputation, prostatic and abdominal surgery, infection, coronary thrombosis, cerebral vascular accident, corticosteroid therapy, barbiturate coma, and the institution of control of the diabetes by insulin or tolbutamide. Although the factors are numerous and varied, they all yielded a similar result; the neuropathies followed in all detail the symptoms, signs, spinal fluid findings and course characteristic of the recognized forms of diabetic neuropathy. This sequence suggests a common pathway, a common pathogenetic mechanism and a cause-effect relationship.

A relatively uniform latent time interval was observed between the

stress factor and the onset of the neuropathy. This latent interval is directly parallel to the time interval that exists in situations wherein neuropathy follows a known inciting factor. The presence of this constant time interval emphasizes the validity of the concept and suggests an operative toxic or metabolic factor as a speculative hypothesis.

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SUMMARIO IN INTERLINGUA

Neuropathia Diabetic Post Situationes de Stress

In iste reporto il es monstrate que un factor additional e non relationate al mesuras del stabilisation de diabete, *i.e.* stress, pote esser un determinante in le disveloppamento de neuropathia diabetic. Le factores stressose que es enumerate e exemplificate include amputation, chirurgia prostatic e abdominal, infection, thrombosis coronari, accidente cerebro-vascular, coma de barbiturato, e le institution del stabilisation de diabete per insulina o tolbutamido. Ben que le factores es numerose e varie, illos omnes produceva un simile resultato, e le neuropathias sequeva in omne detalios le signos e symptomas, le constatationes in le liquido spinal, e le curso clinic que es characteristic del formas recognoscite de neuropathia diabetic. Iste sequentia suggere le existentia de un circuito commun, de un commun mechanismo pathogene, e de un relation de causa e effecto.

Un relativemente uniforme intervallo de tempore latente esseva observate inter le factor stressose e le declaration del neuropathia. Iste intervallo de latentia es directemente parallel al intervallo de tempore que existe in situationes in que le neuropathia seque un cognoscite factor incitatori. Le presentia de iste constante intervallo de tempore sublinea le validitate del supra-presentate interpretation e suggere le hypothese speculative que il se tracta hic del action de un factor toxic o metabolic.

A COMPARATIVE STUDY OF SOME OF THE EFFECTS OF ORAL HYPOGLYCEMIC AGENTS*

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Several years have elapsed since the introduction of the arylsulfonylureas as an adjuvant in the therapy of diabetes. We have had an opportunity to study the effects of the drug "tolbutamide" (Orinase) and the newer drug (Diabinese) "chlorpropamide" in the same group of outpatient diabetics. Chlorpropamide is a new sulfonylurea with substitution of chloride as the initial group of the sulfonylurea molecule. The clinical effect of this new compound is similar to that of tolbutamide but with greater potency (Beaser[1]). The mode of action of these two compounds is still in question; however, it is felt to be similar in both instances. The hypoglycemic effect is apparently mediated through increased production of insulin as a result of stimulation by these compounds of the beta cells of the pancreas (Beaser[2]). However, a specific hepatic effect different from insulin has been demonstrated with tolbutamide. This drug apparently increases the hepatic enzymes which promote glycogen formation and the phosphogluconate shunt (Weber and Cantero[5]).

In our previous report[3] we observed 40 patients, and in over one-half the cases we found an increase in cholesterol despite good control of the diabetes. This paper is concerned chiefly with the control of the same diabetics on chlorpropamide and its effects on the cholesterol serum levels. The cholesterol levels have been investigated by Zeffren and Sherry in 16 diabetics treated with tolbutamide[6] and no particular effect was noted.

Method of Study. Chlorpropamide therapy was given in 32 outpatient diabetic cases. Of these, 22 had been previously treated with tolbutamide. The transition from one compound to the other was abrupt and no change was made in diet or other supportive measures. Patients previously on insulin were started on chlorpropamide in like manner. There were 13 males and 19 females, ranging in age from 21 years to 80 years, with an average age of 60. This study was continued for a maximum of 10 months. The initial dose of chlorpropamide was 1.0 to 1.5 gm., but it soon became evident that this dose was too high, as the earlier patients experienced hypoglycemic reactions. The dosage was then reduced to 0.2 to 0.5 gm., depending on individual response to the drug. None of these patients required hospitalization for control, however several patients hospitalized for other causes were able to continue their therapy without interruption. They were seen as outpatients weekly for one month, and then monthly for the remainder of the study. Complete blood counts, urine examinations, blood sugars and serum cholesterol determinations (Pearson, Stern and McGavack[4]) were done at each visit. Liver and renal function studies were done at least twice on the majority of these patients. Many of these patients had other concurrent illnesses which are summarized in a later table. Each one was carefully interviewed, examined and questioned about side reactions or effects on their other diseases.

*This study made possible by a grant from Pfizer and Company, Inc.

Results. Of the 32 patients included in this study, 6 discontinued therapy for a variety of reasons (see Table 1). Early in the study the dosage was excessive, and 3 patients experienced gastric intolerance with nausea and vomiting and these patients preferred to resume tolbutamide therapy. One patient moved during the course of study and was lost to this series. One patient went into acute congestive failure and chlorpropamide was discontinued, as its effect on sodium retention was not known at that time. A final patient experienced an incompatibility with Diuril (6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide and is designated by the generic name of chlorothiazide) manifested by severe hypoglycemic reactions when the 2 drugs were administered together. When either drug was withheld these symptoms subsided and it was felt that the Diuril was more critical in the management of this case.

Chlorpropamide was found to be a more potent hypoglycemic agent (see Table 2). The average dose of tolbutamide was 1.0 to 3.0 gm. daily, whereas the average dose of chlorpropamide was 0.2 to 0.5 gm. The entire dose of chlorpropamide may be administered in one dose, as it is relatively inert metabolically. Our previous experience with tolbutamide indicated the necessity for divided doses for good control.

TABLE 1.—SIDE EFFECTS WITH CHLORPROPAMIDE THERAPY

Number of Patients	*Symptoms*	*Number of Patients Discontinued*
22	Crystalluria	—
7	Gastric intolerance, nausea, vomiting	3
6	Weakness	—
5	Dizziness	—
3	Glycosuria	—
2	Edema, peripheral	—
2	Incompatibility with Diuril	1
1	Ringing in ears	—
1	Listlessness, lethargy	—
1	Cardiac failure	1
1	Moved away	1
2	Bitter taste in the mouth	—

TABLE 2.—COMPARISON OF TOLBUTAMIDE AND CHLORPROPAMIDE DOSAGE

Dose 24 hr.	*Tolbutamide*	*Chlorpropamide*
.0 to .1 gm.	0	1
.1 to .2 gm.	0	3
.200 to .5 gm.	5	16
.5 to .7 gm.	0	5
.7 to 1.0 gm.	3	3
1.0 to 3.0 gm.	13	1

The body weight of the group taking the drug for an 8- to 10-month period remained stable. There was an over-all gain of 1.4 lb. per patient. This weight change was small and probably of no significance.

The blood sugar determinations initially showed 24 cases to be 150 mg. per 100 ml., or over, on tolbutamide therapy, although none was in excess of 230 mg. per 100 ml. After 6 months of chlorpropamide therapy, 21 cases had blood sugar determinations rang-

TABLE 3.—RESULTS IN 32 PATIENTS TREATED WITH ORAL HYPOGLYCEMIC AGENTS.

Patient	*Previous Diabetic*	*Initial*	*Final*	*Initial Blood Sugar*	*Final Blood Sugar*	*Initial Cholesterol*	*Final Cholesterol*	*Cholesterol Increase*	*Cholesterol Decrease*

TABLE 3.—RESULTS IN 32 PATIENTS TREATED WITH ORAL HYPOGLYCEMIC AGENTS.

Patient No.	*Previous Diabetic Therapy*	*Initial Dosage*	*Final Dosage*	*Initial Blood Sugar mg./100 ml.*	*Final Blood Sugar mg./100 ml.*	*Initial Cholesterol mg./100 ml.*	*Final Cholesterol mg./100 ml.*	*Cholesterol Increase mg./100 ml.*	*Cholesterol Decrease mg./100 ml.*
1	T. 1.0 gm.	1.0 gm.	.4 gm.	170	157	314	216		98
2	T. 1.5 gm.	1.0 gm.	.8 gm.	154	146	408	324		84
3	None	.4 gm.	.4 gm.	279	348	216	233	17	Therapy discont'd
4	T. .5 gm.	.5 gm.	.4 gm.	130	115	324	250		74
5	25 U.NPH	1.5 gm.	.5 gm.	288	126	268	334	66	
6	T. .5 gm.	.25 gm.	.5 gm.	193	141	375	233		142
7	T. 1.5 gm.	1.0 gm.	.5 gm.	290	149	304	296		8
8	20 U.PZI	.4 gm.	.4 gm.	188	118	354	270		84
9	10 U.PZI	.5 gm.	.2 gm.	245	170	258	224		34
10	20 U.NPH	.6 gm.	.4 gm.	153	112	108	128	20	
11	T. 1.0 gm.	.5 gm.	.4 gm.	202	126	344	314		30
12	T. .5 gm.	.5 gm.	.5 gm.	122	123	216	224	8	
13	T. 1.0 gm.	.5 gm.	.8 gm.	105	287	344	523	179	Therapy discont'd
14	T. 1.0 gm.	.5 gm.	.2 gm.	130	112	242	224		18 119
15	35 U.NPH	.6 gm.	1.0 gm.	287	188	415	296		Therapy discont'd
16	T. .5 gm.	.4 gm.	.4 gm.	178	130	242	86		156
17	*Diet-new	.25 gm.	.1 gm.	130	146	344	286		58
18	Diet	1.5 gm.	.6 gm.	264	174	286	258		28
19	T. 2.5 gm.	1.5 gm.	.6 gm.	239	207	415	164		251
20	T. 1.0 gm.	.75 gm.	.6 gm.	207	150	264	304		60
21	T. 1.5 gm.	1.0 gm.	.2 gm.	212	103	324	216		108
22	T. 1.5 gm.	1.5 gm.	.5 gm.	232	138	334	242		92
23	T. 1.5 gm.	1.0 gm.	.4 gm.	157	119	250	258	8	
24	T. 3.0 gm.	1.5 gm.	1.5 gm.	295	224	304	276		28
25	T. 1.5 gm.	.75 gm.	.4 gm.	144	130	396	354		42
26	T. 1.0 gm.	1.0 gm.	1.0 gm.	238	228	334	364	30	Therapy discont'd
27	T. 1.5 gm.	.5 gm.	.2 gm.	104	115	314	258		56
28	T. 1.5 gm.	.4 gm.	.4 gm.	166	162	432	344		88
29	T. 1.5 gm.	.5 gm.	.4 gm.	207	149	470	314		156
30	40 U.NPH	1.5 gm.	.75 gm.	287	150	208	200		Therapy discont'd
31	Diet	1.5 gm.	.75 gm.	357	127	375	286		89
32	T. 1.5 gm.	.75 gm.		167	153	334			Therapy discont'd

T—Tolbutamide.
* —Diet.
Initial Cholesterol and Blood Sugars of Chlorpropamide seen in columns 4 and 6 above also represent the final Cholesterol and Blood Sugar determinations of our Tolbutamide cases.

ing from 103 to 150 mg. per 100 ml. The remaining cases were grouped from 150 to 224 mg. per 100 ml., except where we felt that there was a decided improvement in the blood sugar control with chlorpropamide over the tolbutamide (see Table 3).

The urine examination reflected the blood sugar determinations. These patients were instructed in urine examination for sugars and they uniformly experienced better control of glycosuria on chlorpropamide. Microscopic examination of the urine was done on each clinic visit, and crystalluria was a common occurrence. No other evidence of urinary abnormalities was noted and no impairment of renal function was encountered.

The serum cholesterol changes were the most interesting phase of our study (see Table 3). There were 25 cases in which we found the cholesterol exceeding 250 mg. per 100 ml., 22 cases exceeding 300 mg. and 10 cases exceeding 350 mg. per 100 ml. at the onset of chlorpropamide therapy. All of these patients were surprisingly well controlled on tolbutamide, yet their serum cholesterol levels reflected a serious problem when one considers the normal (125 to 250 mg. per 100 ml. by the method of Pearson, Stern and McGavack) values for healthy people. The higher levels of cholesterol in the previously controlled diabetics on tolbutamide were not reflected clinically. There were no physical symptoms or signs of hypercholesteremia, however one cannot ignore these levels in a diabetic. We were impressed with the values of the cholesterol in the chlorpropamide-treated patients. We found a definite correlation between the lowered blood sugar levels and the cholesterol levels. In 23 patients the cholesterol was also decreased while on chlorpropamide therapy.

The average decrease in serum cholesterol was 82 mg. per 100 ml. Twenty-one of these 23 patients had a significant lowering of blood sugar levels associated with the lowered cholesterol levels. In 7 patients the cholesterol level was elevated an average of 46 mg. per 100 ml. Two of the 7 patients showing an elevation of serum cholesterol levels were poorly controlled and had a concomitant rise in the blood sugar levels. One of these patients discontinued the drug because of nausea, without resuming Orinase or insulin therapy. In a second patient, a juvenile diabetic, control was inadequate and the drug was discontinued. In a third patient, in which an elevation of cholesterol was observed, the drug was discontinued because of gastrointestinal intolerance. In the remaining cases no reason for the increased cholesterol could be found and the increase was so small so as to be felt of no statistical significance.

Discussion. Our experience with the 2 new hypoglycemic agents, chlorpropamide and tolbutamide, seems to indicate that these compounds can afford adequate control for the mild and moderate diabetic. It would seem from this comparative study that control with chlorpropamide is relatively simple and produced a more satisfactory blood sugar and serum cholesterol level than tolbutamide. Chlorpropamide could be administered in one dose in the morning with no adverse effects on control. This drug was more potent, and smaller dosages could be used. This increases the ease of administration as well as reduces the economic factors involved.

Side effects with chlorpropamide therapy have been previously outlined (Table 1). Complications of any serious nature directly attributed to therapy with this drug were not encountered.

Three patients, who were mild diabetics, developed symptoms of weakness, grogginess, awkward gait and depression. There was no particular pattern to these symptoms. We found that the symptoms represented a hypoglycemic effect from overdosage with chlorpropamide in the initial stage of our study. These 3 patients preferred to go back on their tolbutamide therapy rather than continue with chlorpropamide. If they had continued on the reduced dosage, we now feel they could have been easily controlled.

TABLE 4.—CONCOMITANT DISORDERS IN THIS SERIES OF DIABETIC PATIENTS.

Number of Patients	*Disease*
13	Hypertensive cardiovascular disease
7	Arteriosclerotic heart disease
6	Obesity, exogenous
3	Cholecystitis
3	Pulmonary edema
2	Peripheral neuritis
1	Asthma
1	Cancer
1	Cataracts
1	Cystitis
1	Gastritis
1	Hypotension
1	Infected nasopharynx
1	Pneumonitis
1	Polycythemia vera
1	Pruritus vulvæ
1	Psychiatric symptoms
1	Seborrhea dermatitis
1	Sinusitis

When the dosage was adjusted the control of later patients was relatively easy. No significant change in the urinary output, blood studies or liver functions was seen.

Many of the patients used in this series had other diseases (Table 4). Except in the instance previously noted, therapy of the secondary disease was not interrupted or affected by the chlorpropamide. The incompatibility with Diuril was felt to be due to the similarity of their chemical structure. Twenty patients in this study had cardiovascular disease of some degree. In one instance it was felt that the hypoglycemic agent may have precipitated an episode of acute congestive failure, however this was not substantiated by further investigation. It is of interest to note that the patient with polycythemia vera was able to continue on phenylhydrazine therapy and triethylenemelamine without any evidence of incompatibility.

In view of the high incidence of vascular disease in diabetic patients, as reflected in the present series, the role of cholesterol and lipid metabolism attains increased significance. The importance of the high cholesterol level in the etiology of atherosclerotic conditions is not completely defined. However, any drug that either increases or decreases the lipid levels must be considered as a potential problem until the exact etiology of atherosclerosis is understood.

Summary. 1. Thirty-two diabetic patients were investigated, and a new hypoglycemic agent, chlorpropamide, was used to control the diabetes. Twenty-two of these patients were previously treated with tolbutamide.

2. The patients studied were all out-

patients and suffered no serious complications during the 6 to 10 month study.

3. Comparison of the 2 drugs in the same group of patients showed that chlorpropamide produced a better hypoglycemic effect, a lower cholesterol level and increased efficiency of administration.

4. Chlorpropamide affords a prolonged, even hypoglycemic blood level that makes the treatment of mild, moderate, and elderly diabetics a simplification.

ACKNOWLEDGMENT: We are indebted to Mrs. Nellie Hodge, R.N. and to Mr. David D. Heidbrink, M.T., for their technical assistance.

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SUMMARIO IN INTERLINGUA

Un Studio Comparative de Certe Effectos de Oral Agentes Hypoglycemic

1. Trenta-duo diabeticos esseva investigate. Un nove agente hypoglycemic, chlorpropamido, esseva usate in stabilisar le diabete. Vinti-duo del patientes habeva previemente essite tractate con tolbutamido.

2. Omne le patientes studiate esseva patientes visitante. Illes suffreva nulle serie complicationes durante le periodo de 6 a 10 menses del studio.

2. Un comparation del duo mentionate drogas in le mesme gruppo de patientes monstrava que chlorpropamido se distingueva per un plus marcate effecto hypoglycemic, un plus basse nivello de cholesterol, e un meliorate efficacia del administration.

4. Chlorpropamido produce un prolongate e uniforme nivello de concentration in le sanguine. Assi illo simplifica le tractamento de patientes con leve e moderate formas del morbo e etiam de patientes de etate plus avantiate.

THE EFFECT OF TOLBUTAMIDE (ORINASE) ON THE LIVER*

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In 1942, Janbon, while studying the therapy of typhoid fever, found that a thiodiazol sulfonamide was able to cause hypoglycemia in some of the patients (Loubatieres[16]). Following this, Loubatieres and others investigated a number of related compounds and found many to be effective in causing hypoglycemic reactions (Goldberg and Jefferies[11], Loubatieres[17], Macallum[18]). In 1955, the use of p-amino-benzene-sulfonamidobutylurea (BZ55, Carbutamide) for the control of diabetes replacing exogenous insulin was reported (Achelis and Hardebeck[1], Bertram, Benfeldt and Otto[5], Franke and Fuchs[10]). Unfortunately, in 1956 it was shown to be too toxic and its clinical use was discontinued. A similar nonbacteriostatic compound, 1-butyl-3-p-tolylsulfonylurea (D860, tolbutamide, Orinase), also having hypoglycemic effects in diabetic patients, is at present receiving further clinical and laboratory evaluation. This investigation was undertaken to determine the effect of Orinase‡ on the liver.

Material and Methods. Six adult diabetic patients were followed with hepatic function studies while on an Orinase regimen. Liver biopsies were performed on 3 of these patients. The patients in the series consisted of 2 men and 4 women ranging in age from 54 to 77 years. They were placed on the Orinase routine while hospitalized for various problems other than diabetes mellitus. The known duration of the diabetes ranged between 14 days and 22 years. None of these patients had had previous episodes of diabetic coma. In order better to select the patients for the Orinase therapy prior to actually placing them on tolbutamide, an oral "Orinase test" was performed (Camerini-Davalos, Marble and Root[6]). This consisted of cessation of insulin therapy for 3 days. On the morning of the fourth day the fasting blood sugar level was determined, and the patient was then given 3 gm. of the oral hypoglycemic agent. If at the end of 4 hours the blood sugar level had decreased by 20% or more, the chances were that this patient would respond favorably to Orinase. It has been previously demonstrated, however, that this is not a completely reliable test, and that all patients with onset of diabetes past the age of 20 deserve a trial period of tolbutamide before declaring them unsuitable for this regimen (Dolger[7], Levine and Duncan[14]). As it turned out, the diabetes of 2 patients (not presented in this series) with responses of more than 20% was not well controlled after 2 weeks of Orinase therapy, while one patient had a response of less than 20% and was well regulated by Orinase. At no time have any of the patients exhibited either clinical or laboratory toxicity, such as skin rash, malaise, fever, renal dysfunction, red blood cell or white blood cell depression. These patients

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have been on Orinase plus the diabetic diet control for periods of between 82 and 173 days. In all instances, the oral hypoglycemic agent plus diabetic diet were used to replace completely the insulin program. Immediately following the Orinase test, the dosage was reduced daily until by the fourth day a level of 1.0 gm. per day was given. The amount was later varied as deemed necessary.

Hepatic function in each of the patients was followed by carrying out determinations of serum cholesterol and cholesterol esters, total serum protein as well as the serum albumin and serum globulin, the 48-hour cephalin flocculation, bromsulfalein retention and prothrombin time. These values were checked at approximately weekly intervals. In no instance did any of the patients display abnormal hepatic function tests attributable to the Orinase therapy. The values obtained are summarized in Table 1.

TABLE 1.—BLOOD STUDIES: RANGE OF HEPATIC FUNCTION VALUES

Patient	(1) *J.F.*	(2) *M.B.*	(3) *L.S.*	(4) *A.H.*	(5) *J.A.*	(6) *M.D.*
Cholesterol Total mg./100 ml.	302–157	261–179	221–140	229–143	430–221	330–206
Cholesterol Esters mg./100 ml.	200–95	160–120	132–92	124–76	285–114	235–110
Serum Protein Total, gm.%	6.60–4.55	6.60–5.05	7.65–5.65	7.45–5.55	7.35–5.40	6.40–5.20
Serum Albumin gm.%	3.45–2.70	3.75–2.40	3.86–2.45	3.29–2.07	3.55–2.64	3.45–2.45
Serum Globulin gm.%	3.35–1.67	3.12–2.17	4.30–2.65	4.57–2.63	4.29–2.70	4.03–2.00
Cephalin Flocculation 48 hr.	–	–	– to ++	– to tr	–	–
BSP Retention 45 min.	0	0	0	0	0	0
Prothrombin time % of Normal	90–100	90–100	94–100	88–100	90–100	88–100

The succeeding six paragraphs describe briefly each of the patients. It is felt that in a series of this size, individual descriptions would be of greater value than any attempt to group the patients in various ways.

Case Reports. CASE 1. J.F., a moderately obese 54-year-old white man, entered the hospital for repair of an inguinal hernia. A routine urine check coupled with an elevated blood sugar, sluggishness and weight loss of 6 pounds in the past 3 months disclosed a previously undiagnosed case of diabetes mellitus. His diabetes was controlled with 25 units of NPH insulin per day. The fasting blood sugars ranged between 160 mg. and 124 mg. per 100 ml. while on insulin therapy. On the 28th hospital day, the Orinase test was carried out. The response was an 11% drop in blood sugar. Liver biopsy with a Silverman needle was taken after 20 days of Orinase therapy. Control of diabetes was excellent with 1.0 gm. Orinase daily (See Fig. 1).

CASE 2. M.B., a well nourished, not obese, 54-year-old white woman, entered the hospital with generalized arteriosclerosis and peripheral vascular insufficiency. She had had a right mid-thigh amputation two years earlier for gangrene. The diagnosis of diabetes mellitus had been made 22 years ago, and she was controlled on 35 units of NPH insulin per day plus diabetic diet. Her fasting blood sugar levels normally ranged between 110 and 170 mg. per 100 ml. On the 5th hospital day she was given the Orinase test. The response was a 22% drop in blood sugar. A liver biopsy was performed with a Silverman needle on the 26th day of therapy. Control of diabetes was excellent with dosage of 1.0 gm. Orinase daily (See Fig. 2).

CASE 3. L.S., a moderately obese 71-year-old white man, entered the hospital with pansinusitis and atrophic rhinitis. Diagnosis of diabetes mellitus was made after a positive routine clinitest of the urine and a subsequent elevated (175 mg. per 100 ml.) blood sugar

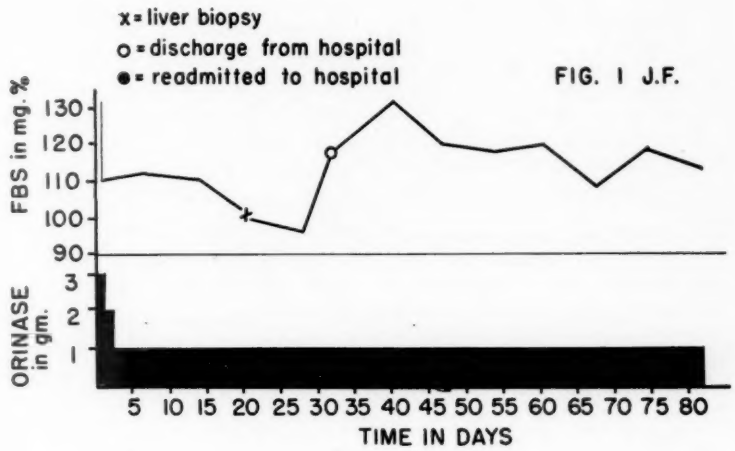

Fig. 1

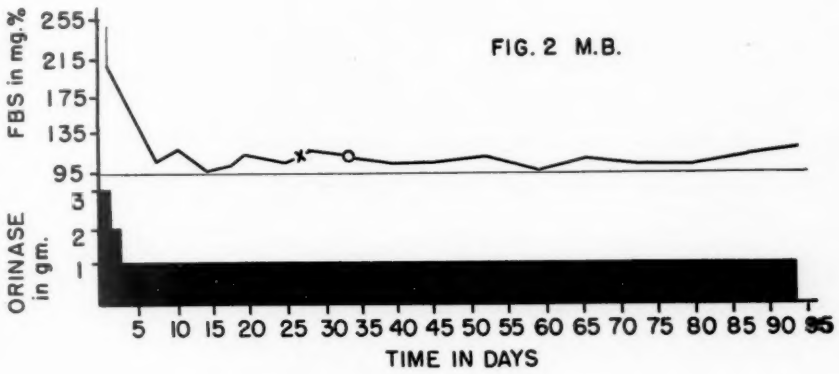

Fig. 2

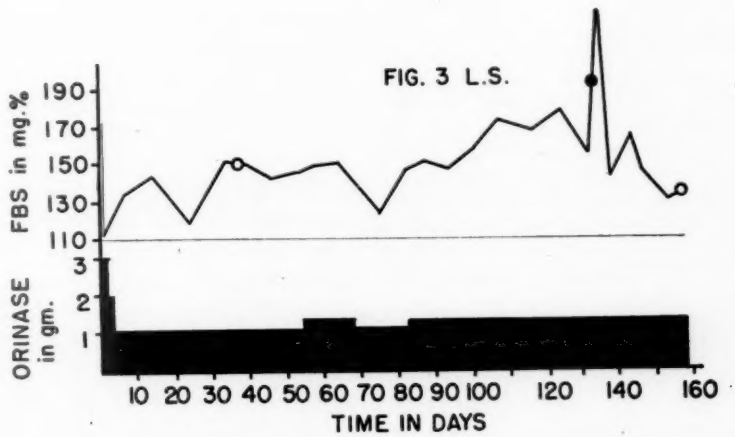

Fig. 3

level. He was at first controlled on 25 units of NPH insulin per day plus diabetic diet. His fasting blood sugar levels normally ranged between 110 and 150 mg. per 100 ml. On the 50th hospital day he was given the Orinase test. The response was a 22% drop in blood sugar. Control of diabetes was satisfactory on 1.25 gm. Orinase daily. (See Fig. 3; readmission to the hospital for congestive failure is indicated.)

CASE 4. A.H., a well nourished, not obese, 64-year-old Negro woman, entered the hospital with a plantar abscess and a diagnosis of endarteritis obliterans. She had had a midthigh amputation of her left leg 3 years ago, and she had been controlled on 20 units of NPH insulin per day plus diabetic diet. Her fasting blood sugar normally varied between 120 and 140 mg. per 100 ml. On the 95th hospital day she was given the Orinase test. The response was a 29% drop in blood sugar. A liver biopsy was performed with a Silverman needle after 113 days of Orinase therapy. Control of diabetes was excellent on dosage of 1.0 gm. Orinase daily (See Fig. 4).

CASE 5. J.A., a slightly obese, 75-year-old Negro woman, entered the hospital with an upper respiratory infection. She had had diabetes for 20 years, and was controlled by 10 units of NPH insulin per day with diabetic diet. Her fasting blood sugar levels normally ranged between 110 and 190 mg. per 100 ml. She had diabetic retinopathy and an occasional cast in her urine. On the 26th hospital day she was given the Orinase test. The response was a 44% drop in blood sugar. Control of diabetes was excellent on dosage of 1.25 gm. Orinase daily (See Fig. 5).

CASE 6. M.D., a moderately obese, 77-year-old white woman, entered the hospital for removal of cataracts. She had hypertension and arteriolar nephrosclerosis. The diagnosis of diabetes had been made 1 year previously. She was controlled by 35 units of NPH insulin per day with diabetic diet. Her fasting blood sugar levels normally ranged between 130 and 170 mg. per 100 ml. On the 27th hospital day she was given the Orinase test. The response was a 40% drop in blood sugar. Control of diabetes was excellent on dosage of 1.25 gm. Orinase daily. (See Fig. 6; readmission to the hospital for a second cataract removal is indicated.)

Three liver biopsies were obtained using the Silverman needle. A portion of each tissue was fixed in Carnoy's solution, and the other part in formalin-calcium chloride solution. The tissues were sectioned at 5 microns, and then stained routinely with hematoxylin-eosin (Figs. 7–9). In addition they were stained for glycogen with Best's carmine (Figs. 10–12), and for lipids with oil red O (Figs. 13–15). All biopsies were taken 2 hours after a normal meal. Tissues were obtained from J.F., M.B., and A.H., as noted above. All of the tissues appear to be well within normal limits, both on the basis of histological appearance and histochemical staining reactions. There are, however, differences within the group. J.F. (Figs. 7, 10, 13) showed a little fatty infiltration with a heavy deposit of lipid droplets and a small amount of glycogen deposition. He also had a very slight amount of periportal round cell infiltration. M.B. (Figs. 8, 11, 14) showed very little fatty change with only an occasional vacuole and a moderate number of stained lipid droplets, with slightly more glycogen deposition than J.F. There was a very minimal amount of periportal round cell infiltration. A.H. (Figs. 9, 12, 15) showed minimal fatty changes with a lesser number of lipid droplets than the other two, and only a rare vacuole. The glycogen deposition in the last case was the heaviest of the 3 patients. There was no evidence of periportal inflammation. The fat and glycogen distribution was uniform throughout the tissues with no peripheral or central lobular pattern. The only apparent reciprocal arrangement was with regards to relative quantity of fat and glycogen. It was noted, in addition to the above findings, that the liver of J.F. showed many nuclear vacuoles, that of M.B. very few, and that of A.H. almost none. These vacuoles were interpreted as glycogen deposition within the nuclei.* However, they did not

*The authors are indebted to Drs. H. W. McFadden and C. A. McWhorter for this and other observations concerning the tissues.

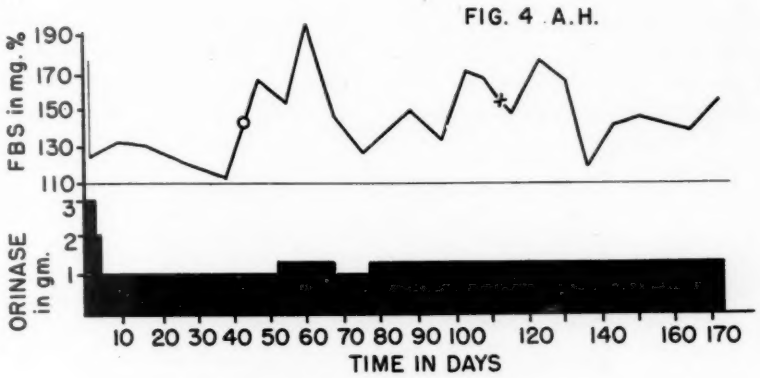

Fig. 4

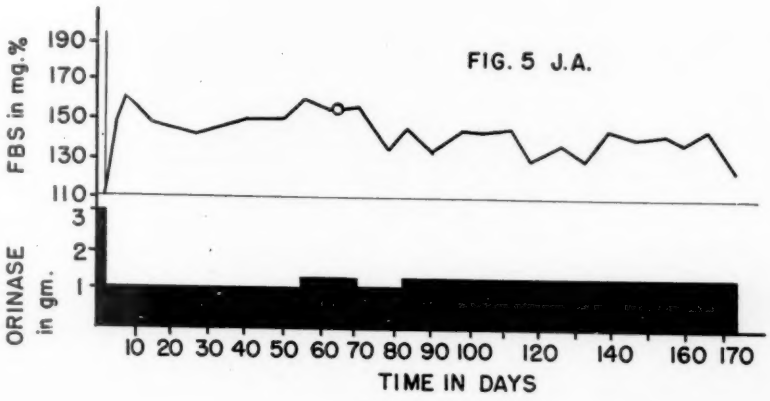

Fig. 5

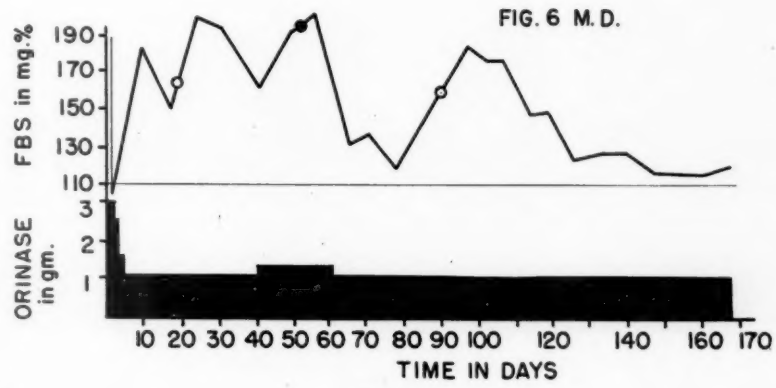

Fig. 6

take the stain for either glycogen or fat. Since intranuclear glycogen vacuoles are not a constant finding in diabetes and since there is no apparent correlation between duration of diabetes, severity of the diabetes, or degree of control and the finding of these vacuoles, little significance was attached to their presence (Warren and Le Compte[25]). All 3 patients did display, however, an occasional, small intra-nuclear granule of glycogen, as

Figure 7, J.F.

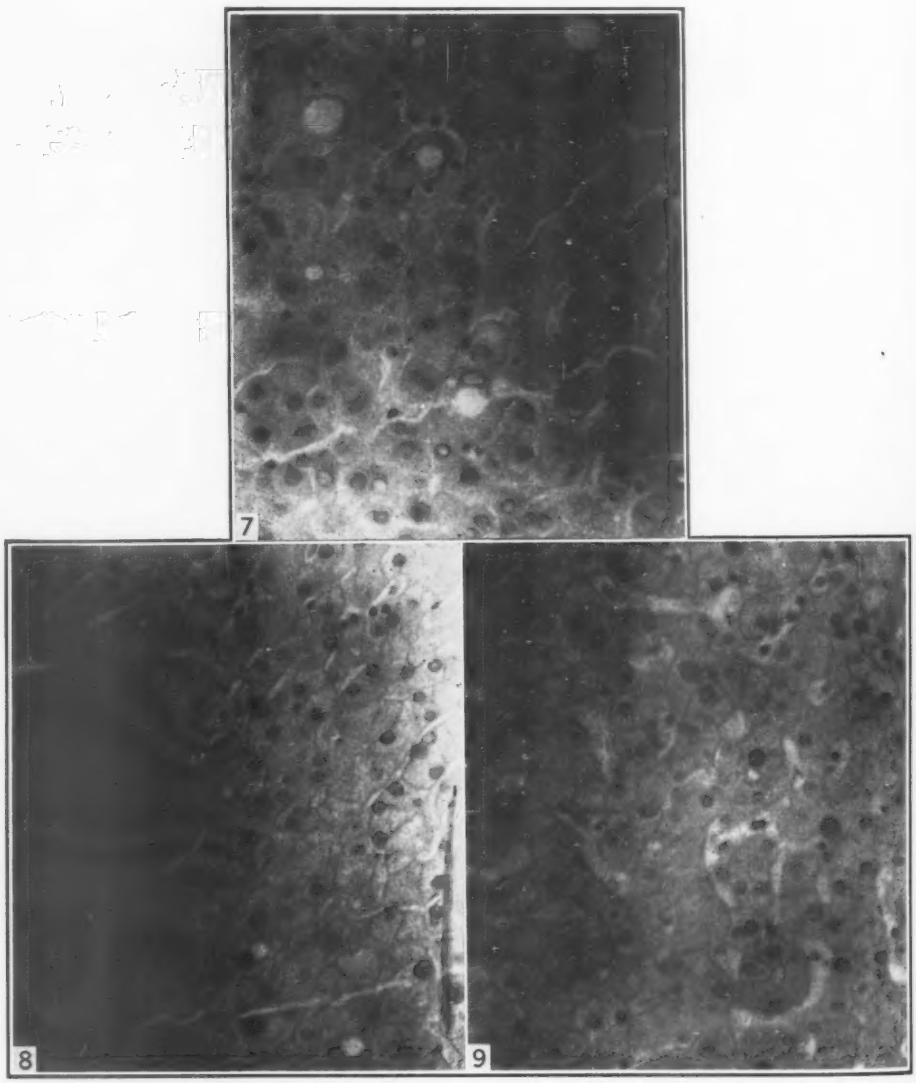

Figure 8, M.B.

Figure 9, A.H.

Explanation: Figures 7, 8, 9. Hematoxylin-eosin stain. It is readily seen that the tissues pictured are essentially normal. J.F. has a few more fat vacuoles than has M.B., while A.H. shows none. × 220.

demonstrated histochemically. There seemed to be no difference between patients, in this respect. None of the biopsy material showed any signs of cytotoxicity.

Discussion. It is beyond the scope of this paper to enter into a discussion of the various possible modes of action of Orinase which have been presented in the literature. The uses and

Figure 10, J.F.

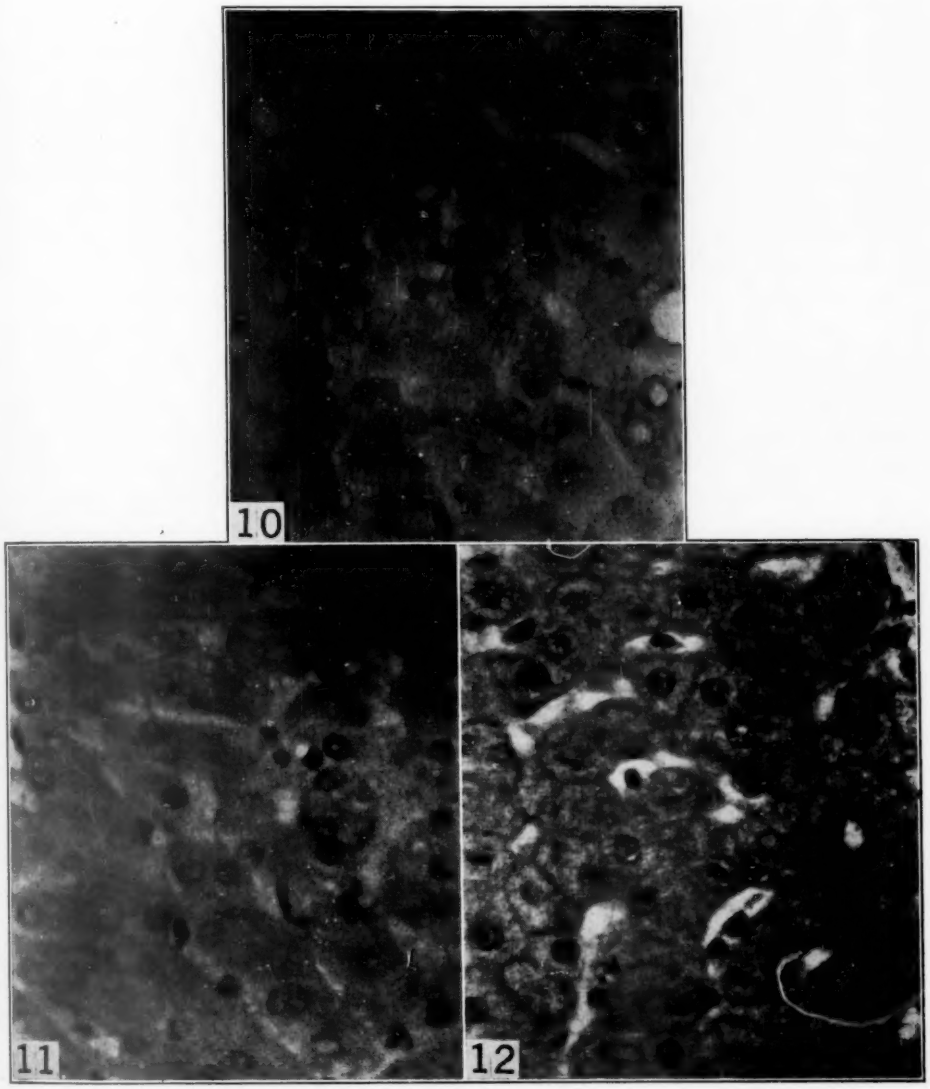

Figure 11, M.B. Figure 12, A.H.

Explanation: Figures 10, 11, 12. Best's carmine stain for glycogen. A.H. is seen to have the greatest amount of glycogen with rather distinct granules of the material. J.F. shows the least glycogen deposition, and M.B. has only a small amount more. The non-staining lipid vacuoles and intra-nuclear vacuoles are apparent. × 420.

limitations of tolbutamide have also been extensively explored. Our main interest is centered about the possible effects which this compound might have upon the liver, especially considering the earlier oral hypoglycemic agent Synthalin and its action by hepatotoxicity with a subsequent derangement of glycogen synthesis (Lewis[15]). Much work has been done to impli-

Figure 13, J.F.

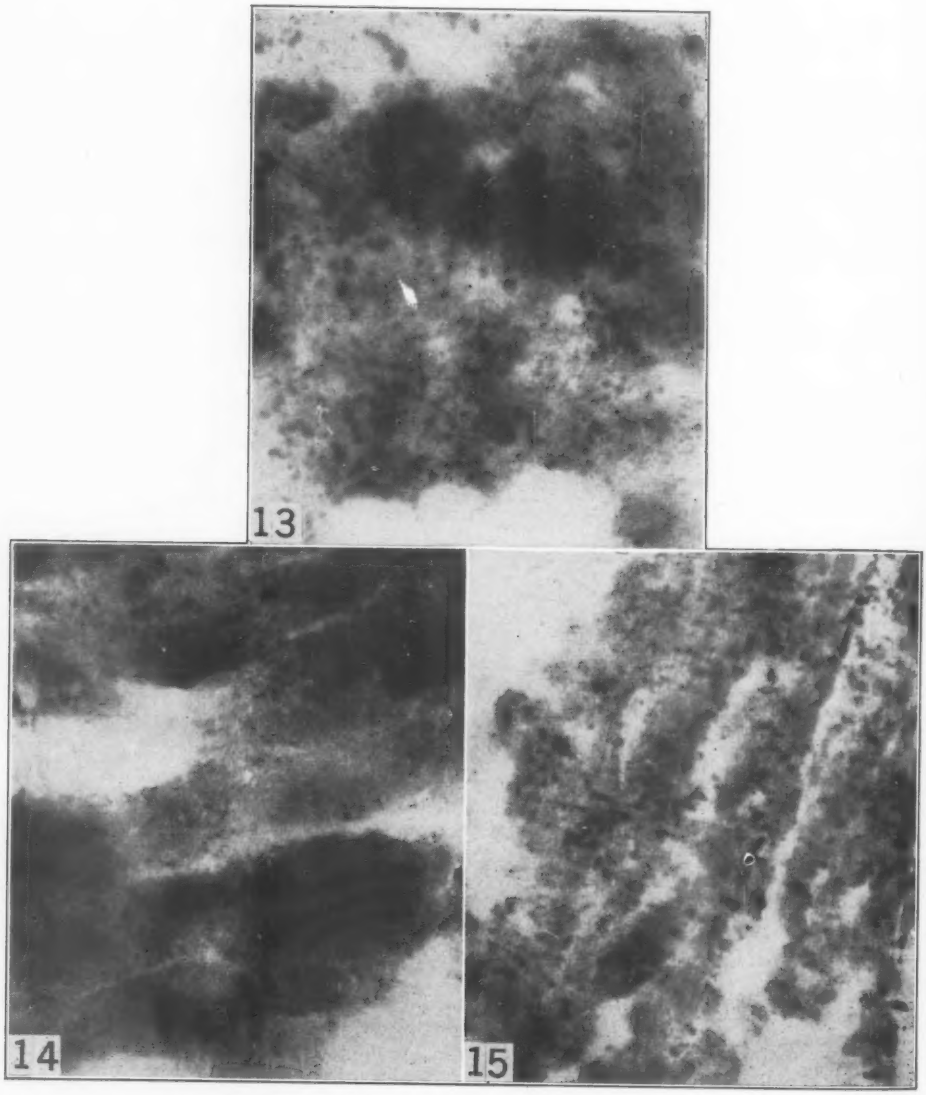

Figure 14, M.B. Figure 15, A.H.

Explanation: Figures 13, 14, 15. Oil red O stain for lipids. The greatest droplet size and concentration are seen in association with the liver of J.F. The least concentration of lipid is seen in the photomicrograph of the liver speciment taken from A.H. The lipid content of the liver of M.B. is between the other two in density, but lies closer to that of J.F. × 420.

cate the liver as one of the sites of action of tolbutamide. It was suggested that tolbutamide inhibited hepatic gluconeogenesis and hepatic release of glucose, or that there was improved hepatic glucose, ketone body and fatty acid utilization (Anderson *et al.*[2], Purnell *et al.*[21], Renold *et al.*[22,23]). It has been fairly well demonstrated *in vitro,* however, that tolbutamide has little effect on glucose-6-phosphatase activity and that the concentration of tolbutamide needed to inhibit glucose production from liver slices is excessively high (Ashmore, Cahill and Hastings[3], Berthet, Sutherland and Makman[4], Vaughan[24]). Dulin and Johnston observed that tolbutamide was able to exert a hypoglycemic effect in hepatectomized animals, and that in fasted, intact animals, tolbutamide caused decreased blood sugar with an increase in liver glycogen content[8]. In normally fed rats, tolbutamide caused decreased blood sugar without changing the liver glycogen, an effect "incidental to the 'insulinlike' ability of tolbutamide to stimulate glucose utilization." No muscle glycogen changes have been observed with tolbutamide administration (Miller *et al.*[19,20]). Other workers have also noted the absence of variation from normal in the liver function tests of patients with both healthy and diseased livers (Elrich and Purnell[9], Knick and Emrich[13]). In the present series there are no abnormalities which can be attributed to Orinase therapy. It should be noted here that the geriatric patient may normally show an inverted or decreased serum A/G ratio (Karel, Wilder and Beber[12]). The results obtained with the liver function studies show no indication of hepatic dysfunction. More concrete evidence of this was seen in the liver biopsy. While all liver specimens appeared to be within normal limits it is interesting to note that the patient receiving tolbutamide for the shortest period of time, 20 days, had the most fatty infiltration and the least glycogen. On the other hand, the patient receiving tolbutamide for the longest period of time, 113 days, had the least fatty infiltration and the most glycogen. The liver of the patient receiving Orinase for 26 days was approximately intermediate between the other two but closer in appearance to the liver of the person on 20 days of therapy. Study of the specimens revealed neither disturbed morphology in general nor cytotoxicity in particular. The livers of these patients are comparable to those of well-controlled diabetic patients receiving only insulin and diabetic diet therapy.

Conclusions. 1) Tolbutamide is a suitable oral hypoglycemic agent for selected, adult diabetic patients. 2) Duration of the diabetes is apparently not well correlated with success or failure of tolbutamide therapy. 3) The oral Orinase test is not a completely accurate criterion for prejudging the efficacy of tolbutamide therapy. 4) Orinase does not cause abnormalities to appear in selected hepatic liver function tests. 5) The content and distribution of lipid and glycogen in the liver of the patient on Orinase therapy are comparable to those of diabetic patients well controlled by insulin. 6) Orinase does not cause abnormal histologic appearance of the liver.

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SUMMARIO IN INTERLINGUA

Le Effecto de Tolbutamido (Orinase) Super le Hepate

1. Tolbutamido es un appropriate oral agente hypoglycemic pro seligite adulte patientes diabetic.

2. Le duration del diabete pare esser pauco correlationate con le successo o non-successo del therapia a tolbutamido.

3. Le test a tolbutamido oral non es un completemente accurate criterio in le prediction del efficacia del therapia con ille agente.

4. Tolbutamido non causa le apparition de anormalitates in seligite tests del function hepatic.

5. Le contento e le distribution hepatic de lipido e glycogeno in patientes sub therapia a tolbutamido es comparabile a illos in patientes con diabete ben stabilisate per insulina.

6. Tolbutamido non causa un anormal apparentia histologic del hepate.

PROTHROMBIN TIME OF CAPILLARY BLOOD FOR OUTPATIENT ANTICOAGULANT THERAPY*

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The test most commonly used in the control of oral anticoagulant therapy is the Quick One-Stage Prothrombin Time. This method is time-consuming and cumbersome in outpatient clinics, where a large number of patients must be tested in a limited time. A simple, practical and shorter modification of the Quick test, using whole blood obtained by finger prick, will be described.

Method. The tip of the patient's finger is cleaned with an alcohol wipe. The arm is then allowed to hang down for a few seconds to ensure a free flow of capillary blood. Using a disposable blood lancet a prick is made in the flesh of the finger tip. The finger is wiped dry with gauze and 0.1 ml. of blood is drawn up in a siliconized pipette in the same manner as blood is obtained for hemoglobin estimation. This blood is immediately blown into a micro test tube containing 0.1 ml. of thromboplastin solution, which has been in a water bath at 37° C. A stop watch is started and the tube containing the mixture is kept in the water bath for the next 10 seconds. It is then removed and tilted at one second intervals. When the clot forms the watch is stopped and the time noted is the capillary prothrombin time.

Results. A. COMPARISON OF PROTHROMBIN TIMES OF CAPILLARY BLOOD AND VENOUS BLOOD. Using the same thromboplastin preparation, the prothrombin time determined by the one-stage method of Quick (venous prothrombin time) was compared with the prothrombin time of capillary blood (capillary prothrombin time). In each subject the comparisons were made by the same technician at the same time.

1. *Capillary Prothrombin Time in Normal Subjects.* Table 1 shows the comparison of the 2 methods in 25 normal subjects. The range of venous prothrombin times was between 14 and 16 seconds. In half the subjects the prothrombin times were identical by the 2 methods, and in the others the difference was 2 seconds or less. The normal range of the capillary prothrombin time was regarded as 15 to 17 seconds.

2. *Capillary Prothrombin Times in Patients Receiving Dicumarol.* In 25 patients receiving Dicumarol, but in whom the venous prothrombin time was only slightly prolonged (17 to 20 seconds) there was close correlation in all but 2 (Table 2).

In anticoagulant therapy a Quick prothrombin time value of 21 to 30 seconds has been considered a relatively safe and effective "therapeutic

*This work was supported by a National Health Grant through the Ontario Heart Foundation.

level." In 50 patients in this range a comparison was made of the prothrombin times done by the two methods (Table 3). It was noted that the capillary prothrombin time tended to be longer than the corresponding venous prothrombin time. This difference became greater as the prothrombin times became longer. It was particularly evident in a group of 15 patients with venous blood prothrombin times over 30 seconds (Table 4).

TABLE 1.—COMPARISON OF PROTHROMBIN TIMES OF VENOUS AND CAPILLARY BLOOD IN 25 NORMAL SUBJECTS

Prothrombin Time in Seconds		*Difference Between Capillary and Venous Prothrombin Times in Seconds*
Venous Method	*Capillary Method*	
14	15	+1
14	15	+1
14	15	+1
14	15	+1
14	15	+1
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	15	0
15	16	+1
15	16	+1
15	16	+1
15	16	+1
15	17	+2
16	15	−1
16	15	−1

Summary

	Venous	*Capillary*
Number of observations	25	25
Range	14 to 16	15 to 17

TABLE 2.—COMPARISON OF PROTHROMBIN TIMES OF VENOUS AND CAPILLARY BLOOD IN 25 SUBJECTS RECEIVING DICUMAROL (WITH VENOUS PROTHROMBIN TIMES IN THE RANGE 17 TO 20 SECONDS)

Prothrombin Time in Seconds		*Difference Between Capillary and Venous Prothrombin Times in Seconds*
Venous Method	*Capillary Method*	
17	16	−1
17	16	−1
17	17	0
17	18	+1
17	18	+1
17	19	+2
17	21	+4
18	17	−1
18	18	0
18	18	0
18	18	0
18	19	+1
18	20	+2
18	20	+2
19	17	−2
19	18	−1
19	21	+2
19	22	+3
20	19	−1
20	19	−1
20	20	0
20	21	+1
20	22	+2
20	20	0
20	29	+9

Summary

	Venous	*Capillary*
Number of observations	25	25
Range	17 to 20	16 to 29

B. EFFECT OF TEMPERATURE ON CAPILLARY PROTHROMBIN TIMES. In order to study the effect of temperature on the capillary prothrombin time, duplicate determinations were performed on 20 subjects (Table 5). One set of tests was made, using a water bath at 37° C. in the manner described above. The

TABLE 3.—COMPARISON OF PROTHROMBIN TIMES OF VENOUS AND CAPILLARY BLOOD IN 50 SUBJECTS RECEIVING DICUMAROL (WITH VENOUS PROTHROMBIN TIMES IN THE RANGE 21 TO 30 SECONDS)

Prothrombin Time in Seconds		*Difference Between Capillary and Venous Prothrombin Times in Seconds*	*Prothrombin Time in Seconds*		*Difference Between Capillary and Venous Prothrombin Times in Seconds*
Venous Method	*Capillary Method*		*Venous Method*	*Capillary Method*	
21	18	−3	25	26	+ 1
21	21	0	25	26	+ 1
21	21	0	25	29	+ 3
21	21	0	25	29	+ 3
21	22	+1	26	26	0
21	22	+1	26	29	+ 3
21	22	+1	26	29	+ 3
21	25	+4	26	29	+ 3
21	26	+5	26	30	+ 4
21	27	+6	26	30	+ 4
22	22	0	26	31	+ 5
22	22	0	26	32	+ 6
22	23	+1	27	25	− 2
22	24	+2	27	26	− 1
22	24	+2	27	39	+12
22	25	+3	28	31	+ 3
22	27	+5	28	31	+ 3
22	28	+6	28	34	+ 6
23	23	0	29	23	− 6
23	24	+1	29	30	+ 1
24	25	+1	29	31	+ 2
24	26	+2	29	34	+ 5
24	28	+4	30	30	0
24	28	+4	30	33	+ 3
24	30	+6	30	41	+11

Summary

	Venous	*Capillary*
Number of Observations	50	50
Range	21 to 30	18 to 41

other tests were conducted without a water bath, with the thromboplastin and blood thromboplastin mixture at room temperature (approximately 25° C.). It was noted that the tests performed at room temperature almost always gave longer values.

C. EFFECT OF HEPARIN ON CAPILLARY PROTHROMBIN TIME. Administration of heparin prolongs the whole blood clotting time and when this is greatly prolonged the prothrombin time of venous blood may also be lengthened. As the capillary prothrombin method was done on whole blood rather than citrated plasma it was thought that heparin might interfere more with the capillary method. As seen in Table 6, the effect of heparin administration on the capillary prothrombin time was no greater than on the venous prothrombin time.

D. REGULATION OF OUTPATIENT DICUMAROL THERAPY WITH THE CAPILLARY

PROTHROMBIN TIME. The capillary prothrombin time has been used as a means of regulating the dose of Dicumarol in 25 outpatients over a 6-month period. As with the venous method, an attempt has been made to maintain the capillary prothrombin time in the range of 21 to 30 seconds. This 6-month period was compared with the preceding 6-month period of these same patients (when the venous prothrombin time was the basis of control). In each of the observation periods the prothrombin times were within the therapeutic range two-thirds of the time and no serious bleeding was encountered.

TABLE 4.—COMPARISON OF PROTHROMBIN TIMES OF VENOUS AND CAPILLARY BLOOD IN 15 SUBJECTS RECEIVING DICUMAROL (WITH VENOUS PROTHROMBIN TIMES OVER 30 SECONDS)

Prothrombin Time in Seconds		*Difference Between Capillary and Venous Prothrombin Times in Seconds*
Venous Method	*Capillary Method*	
31	30	− 1
32	33	+ 1
33	36	+ 3
33	42	+ 9
34	33	− 1
34	40	+ 6
34	54	+20
35	40	+ 5
36	51	+15
37	33	− 4
37	52	+15
45	52	+ 7
46	83	+37
59	73	+14
62	68	+ 6

Summary

	Venous	*Capillary*
Number of Observations	15	15
Range	31 to 62	30 to 83

TABLE 5.—COMPARISON OF CAPILLARY PROTHROMBIN TIMES PERFORMED SIMULTANEOUSLY AT ROOM TEMPERATURE AND AT 37° C. IN 20 SUBJECTS

Capillary Prothrombin Time in Seconds		*Difference Between Determinations Done at 37° C. and Room Temperature*
37° C.	*Temperature*	
15	18	+3
15	19	+4
15	19	+4
15	20	+5
15	21	+6
15	21	+6
15	21	+6
15	21	+6
16	19	+3
16	20	+4
16	23	+7
20	24	+4
21	24	+3
22	26	+4
22	27	+5
29	36	+7
31	38	+7
41	43	+2
52	58	+6
54	59	+5

Summary

	37° C.	*Room Temperature*
Number of observations	20	20
Range	15 to 54	18 to 59

TABLE 6.—COMPARISON OF PROTHROMBIN TIMES OF VENOUS AND CAPILLARY BLOOD IN 8 SUBJECTS RECEIVING HEPARIN

Patient	*Whole Blood Clotting Time (Lee-White Method) in mins. Normal 9 to 11 mins.*	*Prothrombin Time in Seconds*	
		Venous Method	*Capillary Method*
1	14	17	17
2	15	16	16
3	16	15	16
4	16	16	15
5	30	16	20
6	44	21	15
7	>60	23	20
8	>60	26	21

Discussion. The use of capillary blood for the estimation of prothrombin time has been described by a number of investigators (Hoffman[1], Manchester and Rabkin[3], Quick[4], Smith *et al.*[5]). Manchester found his modification[2] to be a satisfactory means of controlling outpatient anticoagulant therapy.

The chief difference in the present method is the more careful control of temperature. At room temperature the results were longer than at 37° C. In order that the results be comparable, the temperature of the clotting mixture must be kept constant by means of a water bath.

The end point of the test was sharp and reproducible. The average time required to complete a test was less than 2 minutes, making it very suitable for outpatients who could be given immediate instructions concerning the dose of the anticoagulant drug and the date of the next appointment. When venous prothrombin times were performed in large numbers in the Outpatient Clinic, there was always a minimum delay of half an hour between the taking of the blood and the final instructions to the patient, and sometimes much longer.

The presence of tissue juice, a powerful thromboplastic substance, has been a theoretical disadvantage to prothrombin times done on blood obtained by finger prick. In this study the close agreement between the prothrombin times of venous and capillary blood in the same normal subject suggested that tissue juice was not an important variable. It is assumed that the excess of rabbit brain thromboplastin masked the activity of the tissue juice.

When the venous prothrombin time was normal or only slightly prolonged by Dicumarol therapy, there was close agreement between the venous and capillary methods. However, when the venous prothrombin time was more prolonged (25 seconds or longer) a divergence was noted, in which the capillary prothrombin time tended to be longer. The reason for this is obscure, but might be due to the coagulant effect of citrate added to the venous blood sample. If this is so, capillary blood prothrombin times may reflect more accurately the changes produced by oral anticoagulant drugs.

Summary and Conclusions. 1. A method is described for the estimation of the prothrombin time of capillary blood obtained by finger puncture.

2. With this test the result is available in less than 2 minutes. Venipuncture, the addition of citrate solution and the use of a centrifuge are not required.

3. The temperature of the clotting mixture should be controlled in a water bath at 37° C.

4. The method has been found to be satisfactory for the control of anticoagulant therapy in outpatient clinics.

5. Close agreement with venous prothrombin times was found in the same subject when the venous prothrombin time was normal or slightly prolonged. With longer venous prothrombin times the value for capillary blood tended to be longer than that obtained on the venous sample.

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(Interlingua on page 455)

TOBACCO SMOKING AND BLOOD COAGULATION: ACUTE EFFECT ON PLASMA STYPVEN TIME*

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Epidemiological reports showing an association of smoking habit with coronary heart disease mortality have revived interest in the circulatory and metabolic effects of tobacco smoking (Doll and Hill[2], Hammond and Horn[5]). Smoking produces marked circulatory responses in most individuals, reflected in pulse rate, arterial blood pressure, and peripheral blood flow. These acute responses may conceivably play a role as precipitating factors in patients with angina pectoris or coronary artery disease, but in themselves provide no real basis for conjecture about the pathogenesis of coronary heart disease. There is no direct evidence that smoking accelerates atherogenesis or thrombogenesis.

However, the rapid hemodynamic changes following inhalation of tobacco smoke are believed to be mediated via nicotine stimulus to autonomic release of epinephrine. Moreover, there are studies which suggest that epinephrine accelerates the coagulation of blood (Cannon and Gray[1], Forwell and Ingram[3]). Coagulability of the blood is unquestionably of great significance in the often rapid clinical event of coronary occlusion, if not in the underlying process of atheroma formation. It is, therefore, pertinent to investigate the acute effect of tobacco smoking on coagulation.

Grassi and Caltabiano[4] have reported shortening of recalcified plasma time, augmentation of prothrombin activity and utilization, shortened clot retraction time, and increased platelet count, after smoking one cigarette. Their study purports to show this shortening is greater in patients with cardiovascular disease than normals but they provided no statistical treatment, and the study is entirely without control in regard to smoking. Hammond[6] has recently intimated on the basis of preliminary experiments that "cigarette smoking results in a decrease in the clotting time of the blood; but this has

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not yet been established with certainty."

Recalcified plasma "Stypven time" has found wide application in study of states of hypercoagulability. The technique is highly reliable and the system is apparently very sensitive to experimental manipulation of environmental factors. (O'Brien[7], Poole and Robinson[9], Orma, Rhodes and Keys[8]). The meaning of changes in this artificial system employing a thromboplastin from Russell's viper venom is not at all clear, and its resemblance to the thromboplastin system operating in man is under scrutiny in this Laboratory. But the Stypven time is more sensitive to some coagulation accelerating factors than the ordinary whole blood or recalcified plasma clotting times and its great technical advantages led us to apply it to this question.

Material and Methods. Two sets of controlled experiments were carried out, one with 16 adult schizophrenic men in a metabolic ward of Hastings State Hospital, the other with 8 young university students. Each group was tested on 2 days, in the fasting state, and those who were smokers on the first day became controls on the second, in a crossover double-controlled procedure. All were habitual smokers and had refrained from eating or smoking overnight, with 14 hours' abstinence in the men at Hastings and 8 to 10 hours in the students. The men at Hastings remained in bed during the experiments, the students reported to the Laboratory in the early morning and sat quietly reading for half an hour before the start of the experiment. Pulse rates were recorded after which the first blood sample was taken. Blood was let by sharp No. 18 needles and rubber tubing, the first 3 ml. being allowed to flow freely into a separate tube and discarded. Nine milliliters of blood was collected in 1 ml. of 3.8% sodium citrate solution, and was spun at 2000 rpm for 30 minutes. All equipment in contact with blood or plasma (needles, rubber tubing and tubes) was siliconized with Siliclad (Clay-Adams, Inc., New York).

Half of the subjects on each experimental day then chain smoked 2 standard brand, regular length, non-filter cigarettes ("found by authoritative independent testing" to contain the *highest* nicotine content of standard U.S. brands, yielding approximately 3 mg. of nicotine per cigarette in the mainstream smoke). Pulse rates were again recorded on all subjects and the second blood letting performed 45 minutes after the first and within 2 minutes of completion of smoking. Plasma samples were identically treated, and stood for the same length of time at each stage of spinning, pipetting, and resting in the water bath.

Plasma clotting time at 37° C. was measured by a photoelectric technique after addition of 1.0 ml. "Stypven" reagent (0.5 mg. "Stypven" Burroughs-Wellcome & Co., dissolved in 10 ml. of 0.9% saline and 5 ml. $CaCl_2$ 0.05M) to 0.5 ml. of plasma (Orma, Rhodes and Keys[8]). The method gives highly reproducible results (standard error of measurement in 422 pairs of replicate determinations was 0.81 seconds where $S.E.M.2 = \Sigma(\Delta^2)/2N$, where $N = 422$ here) and samples were measured in duplicate.

Results. Because of the excellent control of rest, eating, and smoking in the Hastings men, results are considered more reliable in that group. Table 1 shows a trend, not significant, toward shortened plasma "Stypven" time in controls *and* smokers, on both experimental days. There is no significant difference in shortening between those who smoked and the controls. Table 2 shows that no significant changes occurred in the students as controls or after smoking.

That a "nicotine-epinephrine" effect was active from the smoke inhalation is apparent in Table 3 with highly significant rises in pulse rate in the smokers compared to the controls.

Individual changes in coagulation time after the smoking test bear no consistent relationship to the magnitude of the pulse pressor response.

Summary. In 2 crossover controlled experiments involving 16 men living in a metabolic ward and 8 young university students, no significant acute effect of cigarette smoking was found upon the blood coagulation as measured by recalcified plasma "Stypven" time.

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TABLE 1.—PLASMA "STYPVEN"-TIME, IN SECONDS, IN 16 HASTINGS' SUBJECTS IN CROSS-OVER EXPERIMENT ON 2 DAYS

	Control Test			*Smoking Test*		
Subject No.	*Before*	*After*	Δ *A–B*	*Before*	*After*	Δ *A–B*
1	——	——	——	31.7	30.9	−0.8
2	37.1	38.7	+1.6	40.7	38.8	−1.9
3	37.6	30.7	−6.9	33.2	31.6	−1.6
4	44.3	40.2	−4.1	44.4	37.7	−6.7
5	37.5	38.6	+1.1	35.3	36.2	+0.9
6	39.6	38.3	−1.3	30.8	39.3	+8.5
7	30.8	31.5	+0.7	36.9	35.1	−1.8
8	29.7	28.3	−1.4	31.9	30.0	−1.9
9	37.7	37.5	−0.2	42.1	42.8	+0.7
10	38.5	37.9	−0.6	46.3	40.2	−6.1
11	43.7	40.7	−3.0	39.0	32.1	−6.9
12	43.0	39.6	−3.4	44.2	39.4	−4.8
13	37.5	40.1	+2.6	37.7	40.3	+2.6
14	33.4	32.2	−1.2	——	——	——
15	40.1	39.6	−0.5	44.3	42.4	−1.9
16	23.9	25.2	+1.3	23.1	23.6	+0.5
	Mean change = −0.96 sec.			Mean change = −1.33 sec.		
	t = 1.375			t = 1.379		
	p = 0.13			p = 0.18		

Δ Control vs. Δ Smoking
Mean = 0.37
t = 0.43
p = 0.68

TABLE 2.—PLASMA "STYPVEN"-TIME, IN SECONDS, IN 8 STUDENTS IN CROSS-OVER EXPERIMENT ON 2 DAYS

	Control Test			*Smoking Test*		
Subject No.	*Before*	*After*	Δ *A–B*	*Before*	*After*	Δ *A–B*
1	28.5	26.9	−1.6	32.2	33.5	+ 1.3
2	27.0	26.9	−0.1	23.0	24.9	+ 1.9
3	42.5	39.7	−2.8	51.7	40.1	−11.6
4	33.5	31.2	−2.3	43.8	36.4	− 7.4
5	25.9	24.9	−1.0	27.9	23.5	− 4.4
6	27.7	29.7	+2.0	35.3	29.1	− 6.2
7	20.4	21.6	+1.2	28.4	29.6	+ 1.2
8	48.5	49.2	+0.7	42.0	38.6	− 3.4
	Mean change		−0.49			− 3.58

Δ Control vs. Δ Smoking
t = 1.987
p = .09

TABLE 3.—PULSE RATE CHANGES, BEATS PER MINUTE, IN HASTINGS' SUBJECTS. CONTROLS AND SMOKERS

Subject No.	*Control Test*			*Smoking Test*		
	Before	*After*	Δ A–B	*Before*	*After*	Δ A–B
1	60	60	0	64	84	20
2	80	80	0	72	88	16
3	68	80	12	80	84	4
4	60	56	− 4	60	80	20
5	72	72	0	58	64	6
6	56	52	− 4	64	76	12
7	56	52	− 4	44	52	8
8	64	60	− 4	64	76	12
9	96	80	−16	72	68	− 4
10	68	72	4	80	88	8
11	64	60	− 4	64	72	8
12	60	60	0	60	64	4
13	72	60	−12	64	68	4
14	60	68	8	60	68	8
15	72	68	− 4	60	68	8
16	60	56	− 4	64	76	12
Mean pulse change			− 2.0			+ 9.1

Δ Control vs. Δ Smoking
t = 5.49
p = <.0001

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SUMMARIO IN INTERLINGUA

Le Fumar de Tabaco e le Coagulation del Sanguine: Acute Effectos Super le Tempore Coagulatori de Plasma a Stypven

In 2 experimentos con 16 homines habitante un section metabolic e 8 juvene studentes universitari—ambe gruppos serviente alternantemente como gruppo experimental e gruppo de controlo—nulle significative effecto acute del fumar de cigarrettas esseva notate in le coagulation del sanguine secundo mesurationes in plasma recalcificate e pretractate con stypven.

EFFECT OF ANTIDIURETIC HORMONE ON SWEATING AS A PROOF OF ITS EXTRARENAL ACTION

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It is generally accepted that the antidiuretic hormone (ADH) exerts its action on the distal kidney tubules (Maxwell and Breed[5], Smith[8]). In its presence, water is reabsorbed from the tubular lumen into the blood vessels, that is, the ADH protects the organism against water loss.

In this connection the very important question arises whether the ADH is concerned with the water metabolism exclusively at the renal level or controls the water economy of other tissues as well. Some data are recorded herein on sweat secretion that seem to prove an extrarenal effect of ADH.

To decide this question it was necessary to compare the amount of sweat produced in total absence of ADH with that produced in the presence of a known quantity of ADH. For this purpose an experimental subject needed to be found who did not possess ADH of his own. In normal individuals ADH disappears only during water diuresis (for example, water loading). This, however, could not be taken into consideration partly on account of its unsteadiness and partly because water-loading interferes with the fluid balance of the organism. Examinations, therefore, were performed on a patient with diabetes insipidus in whom it had been previously stated that antidiuretic hormone was not produced under any circumstances. To make sure of this, plasma ADH-determinations had been made during the time of thirst, according to the method previously recorded (Hankiss[2]).

Methods and Material. SELECTION OF PATIENT. It was felt that only total diabetes insipidus could be utilized in this study, thereby excluding cases of partial diabetes insipidus such as those recorded by Kourilsky[4]. Also a young patient was to be looked for. The so-called idiopathic (primary) type was preferred to symptomatic (secondary), because lesions of other organs in the secondary type could distort the results.

V.F., a 28-year-old male patient was, therefore, selected. He had had diabetes insipidus for 18 years. He did not know of any significant previous disease. He did not drink alcoholic beverages and smoked 10 to 15 cigarettes a day.

He was a bed-patient in our clinic first from October 22 to November 27, 1958, where the diagnosis was ascertained after a detailed examination. He had been treated for 16 years with several medicaments. In the last 6 years he had been a bed-patient in different hospitals. While under treatment the daily urine output was 5 to 6 liters. He had not been treated for one year. Since then his daily water consumption amounted to 12 to 14 liters. He was feeble and nervous, but without complaints of special organic disease.

The 24-hour urine output was 12 to 13 liters. The specific gravity was 1.001, otherwise the urine examination was negative. Specific gravity did not increase even during thirsting, though hemoconcentration took place. No other internal, ophthalmological or neurological abnormalities were found.

Plasma ADH determinations were carried out at the maximum of thirst (Hankiss[2]). A healthy person thirsting for 12 hours served as a control. While ADH increase could be demonstrated in the normal individual, no antidiuretic effect was obtained with the plasma of the patient. So it became evident that the patient was incapable of producing ADH and thus he proved an ideal subject for further examinations.

To examine the water excretion of the skin, the rubber glove method was used. The gloves had been carefully weighed. They were

drawn over both hands. The hands of the patient were then placed into a streaming water bath at 43° C. for 30 minutes. During the examination the patient was sitting in a comfortable position. It was carefully observed that the hands of the patient should be in water down to the same depth at each examination. After 30 minutes the exterior of the gloves was wiped dry and the gloves taken off while the patient's hands were downwards. The gloves were again weighed with the collected sweat inside. The difference in the weight showed the total of the excreted sweat and the insensible water loss. Sodium and potassium determinations were also carried out from the collected sweat. Therefore, both the gloves and the hands were rinsed with distilled water.

The basic value was determined on a day when neither ADH nor any other therapy had been given to the patient for 24 hours. Next day the examination was repeated 30 minutes after a subcutaneous injection of 3 or 4 units of Pitressin.*

The examination both with and without ADH was repeated 6 times. The examinations were performed at 6 P.M. and at noon.

Results. In Table 1 the volume of the sweat produced in 30 minutes is given in average value for both hands, without ADH.

TABLE 1.—QUANTITY OF SWEAT EXCRETED IN 30 MINUTES IN TOTAL LACK OF ADH AND IN ITS PRESENCE (MEAN VALUES OF 6 EXPERIMENTS EACH)

	With ADH	*Without ADH*
Right hand	7.4 ml.	12.7 ml.
Left hand	6.9 ml.	13.5 ml.

As is seen, the volume of sweat produced after ADH administration is significantly less than without it. Considering that the patient did not have ADH of his own, the basic experiment gave the volume of sweat produced without ADH. It was furthermore possible to observe the effect of a known quantity of Pitressin. The dose was fixed according to the known physiological and therapeutic rate.

*Parke, Davis & Co., Ltd.

Two units of Pitressin were also tried. The sweat excretion was significantly less even with such a small dose.

Concerning the water an orderly and consistent change was observed while it was quite different with the electrolytes (Table 2).

TABLE 2.—COMPARATIVE DATA ON ELECTROLYTE LOSS BY SWEAT. ABSOLUTE VALUES OF SODIUM AND POTASSIUM EXCRETED IN 30 MINUTES, EXPRESSED IN MG.

	With ADH		*Without ADH*	
	Sodium	*Potassium*	*Sodium*	*Potassium*
Right hand	15.6	30.3	9.12	24.5
Left hand	11.0	41.4	13.0	40.0

The absolute value of sodium and potassium excreted with the sweat was the same in the presence or absence of ADH, only their degree of concentration varied in inverse ratio to the quantity of sweat, that is, under the influence of ADH the sodium and potassium were excreted in a more concentrated solution. It is an indication that Pitressin does not affect the electrolyte excretion of the skin. This represents a datum pointing again to the fact that skin can store and excrete water as well as electrolytes independently from each other (Jadassohn[3]).

Discussion. The skin has long been considered as a "second kidney." It is enough to realize that 24% of the water loss of the organism, and 50% of the extrarenal water loss falls to the skin. This is why the effect of ADH was examined and it was found that in physiological doses it significantly decreased the water loss of the skin. The hormone, consequently, exerts a protective effect against water loss. The reaction of the skin shows a similarity to that of the kidney in respect to fluid trans-

port which is completely independent of electrolyte transport. Thus, Pitressin showed a specific hormone effect in selectively decreasing the water loss of skin without influencing the sodium and potassium excretion.

The mechanism by which this protective effect of ADH is enacted in the skin is yet to be elucidated. It was demonstrated by Moog in 1926 that neither the sweat excretion nor the insensible water loss can be proportioned to the dilatation of skin capillaries[6]. The question arises whether the mechanism of ADH is similar in the sweat glands to that in the kidney, that is, whether the sweat produced becomes reabsorbed from the glandular lumen under ADH-effect. For the time being this is but an hypothesis to be decided on through further investigations.

Our researches do not suggest that patients with diabetes insipidus sweat in an increased amount. Our experimental conditions created specific circumstances. Under normal conditions it is probable that the correlation between skin and kidney is prevailing in an increased measure making use always of the kidney and skin according to the requirements of the organism to keep its water economy balanced. As has been mentioned 24% of the water loss of a resting organism falls to the skin, mainly in the form of insensible water loss. At hard physical stress, however, the proportion falling to the skin is significantly greater. In an extreme case 2500 ml. sweat may be produced in an hour. Under such circumstances, naturally, the water excretion of the kidney strongly decreases both in absolute and relative measure.

The situation is just the opposite in diabetes insipidus. Here the relative deficiency of water in the organism must be taken into consideration as a factor which may influence the water balance of subcutaneous tissue (Moog[7]).

The above mentioned correlation of skin and kidney can be insured only by a higher correlating mechanism. This mechanism was searched for in the antidiuretic system. On the basis of the results obtained it may be suggested that the antidiuretic system controls the whole water economy of the organism. This control is not limited to the kidney alone, as has been believed, but it aims to preserve water in other parts of the organism as well. The antidiuretic system is thus not simply antidiuretic, namely impeding water loss in the kidneys; its complex activity tends to make the organism economize on its given fluid reserve, to restrict the water loss in any part of the organism. Generally speaking ADH may be considered a water protecting (preserving) hormone.

Summary. In a patient with diabetes insipidus, who did not have ADH of his own, it was demonstrated, that during deprivation of antidiuretic hormone the volume of the sweat produced was greater than in the presence of ADH. Thus the extrarenal effect of ADH appears established as well as the overall part that the hormone plays in the organism: its complex effect is to insure the water reserve of the organism. Presumably it can be considered in a general sense, a water-protecting hormone.

ACKNOWLEDGMENT: I am indebted to Parke, Davis & Co. for the generous supplies of Pitressin.

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SUMMARIO IN INTERLINGUA

Le Effecto de Hormon Antidiuretic Super le Sudation Como Prova de su Activitate Extrarenal

In un patiente con diabete insipide qui non habeva hormon antidiuretic de origine endogene, il esseva demonstrate que durante le privation de exogene hormon antidiuretic le quantitate del sudor producite per le patiente esseva plus grande que in le presentia de hormon antidiuretic. Assi il pare que le effecto extrarenal de hormon antidiuretic es establite si ben como le rolo que debe esser ascribite a illo in le organismo in general. Iste rolo consiste in le complexe effecto que illo assecura le reservas de aqua del organismo. Il pare que illo pote esser considerate, in un senso general, como un hormon hydroprotectori.

SUMMARIO IN INTERLINGUA

(See page 443 for original article)

Un Test del Tempore de Prothrombina de Sanguine Capillar pro Objectivos de Therapia Anticoagulante in Patientes Visitante

1. Es describite un methodo pro le estimation del tempore de prothrombina de sanguine capillar obtenite per puncturation de un digito.

2. Per medio de iste test, le resultato es disponibile intra minus que 2 minutas. Venipunctura, le addition de un solution de citrato, e le uso de un machina centrifuge non es requirite.

3. Le temperatura del mixtura coagulatori debe esser regulate in un baniomaria a 37 C.

4. Le methodo se ha provate satisfactori in le regulation del therapia anticoagulante in clinicas pro patientes visitante.

5. Un intime concordantia con le venose tempore de prothrombina esseva constatate in le mesme subjecto quando le venose tempore de prothrombina esseva normal o levemente prolongate. Quando le venose tempores de prothrombina esseva plus longe, le valores pro sanguine capillar monstrava le tendentia de exceder illos obtenite pro specimens venose.

HYPOPITUITARISM DUE TO HYPOTHALAMIC SARCOIDOSIS*

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Hypopituitarism commonly results from destructive or expanding tumors within or encroaching upon the sella turcica, or from pituitary apoplexy (Sheehan's syndrome). On rare occasions, granulomatous involvement of the pituitary gland has been reported to result in hormonal insufficiency of either or both the anterior and posterior portions of this gland. Tuberculous meningitis, tuberculomas and syphilitic gummata have likewise resulted in hypopituitarism. The subject of granulomatous lesions of the pituitary gland has been reviewed (Bleisch and Robbins[1], Rickards and Harvey[9]).

Sarcoidosis of the pituitary gland and base of the brain is a rare cause of a clinical syndrome simulating a space occupying lesion of the pituitary gland with or without resultant hypopituitarism (Bleisch and Robbins[1], Glass and Davis[2], Jackson and Hood[3], Jefferson[4], Kraus[5], Magnus[6], Meyer, Foley and Campagna-Puito[7], Owen and Henneman[8], Rickards and Harvey[9]). However, reports of this unusual occurrence are so uncommon that the nature and extent of the hormonal insufficiencies have not been clearly defined nor the response to steroid hormone therapy evaluated. The following case history describes a patient with sarcoidosis of the optic chiasm and hypothalamus simulating a suprasellar space occupying mass and producing clinical signs and symptoms of both anterior and posterior pituitary insufficiency in the presence of an intact pituitary gland.

Case Report. A 27-year-old housewife was admitted to the Peter Bent Brigham Hospital on August 18, 1956, because she was "acting funny." Past history revealed that in 1949, during her first pregnancy, a large spleen was noted and surgically removed because of its "hazard to pregnancy." Pathologic examination was reported as negative. During the early postpartum period, the patient had two spontaneous convulsive seizures which were unexplained. In 1954, the patient first noted an increase in weight of approximately 40 pounds, from an average weight of 125 pounds to 165 pounds, and her menstrual periods ceased. She often complained of sluggishness and easy fatigability. Despite a rather rigid dietary program she had difficulty losing weight.

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†Investigators for the Howard Hughes Medical Institute.

She was seen at another hospital one year prior to admission where examination was reported to reveal no significant abnormalities; however, "pituitary trouble" was among the diagnoses considered as a possible cause of her amenorrhea. Four months prior to admission the patient noted a marked increase in her fluid intake associated with swelling of her ankles. Occasional transient diplopia was also experienced. Examination at that time was said to have revealed a liver 4 finger breadths enlarged and the patient was told that she had cirrhosis of the liver. A rigid dietary program resulted in the loss of approximately 30 pounds, but this weight was rapidly regained. One month before entering this hospital, digitalis therapy was instituted. Small skin lesions were noted by the patient and were subsequently described as "dry areas." She also noted the frequent occurrence of severe headaches accompanied by blind spots, nausea and vomiting. For 2 weeks prior to admission the patient became increasingly lethargic, confused and ultimately stuporous. During this period her fluid intake approximated 4 to 6 quarts daily.

Family history and the remainder of the past history and systems review were noncontributory. The patient was born in Massachusetts and had always resided there.

Physical examination on admission revealed an obese, disoriented, lethargic woman who was markedly dehydrated and unable to respond coherently to questioning. Her obesity was generalized; there was no cervical "hump." A few silver striae were present on the abdomen. There was no axillary hair and scanty pubic hair. The pubic escutcheon was female. There were several small, flat, atrophic, pearly, plaque-like areas over the skin of the upper arms measuring approximately 1 cm. in diameter. The hair follicles in these atrophic skin areas were prominent despite the absence of hair. There was no clubbing or cyanosis. There was one plus pretibial pitting edema. There were no obvious defects in the cranial bones or any musculoskeletal abnormalities. No hemorrhages, exudates, cytoid bodies or other retinal lesions were noted. There was thought to be slight nuchal rigidity or resistance on initial examination. There was no generalized or localized lymphadenopathy. The chest was clear to auscultation and percussion. The heart was of normal size with a grade one apical systolic murmur, quiet heart sounds and regular rhythm. The liver edge was palpable 4 finger breadths below the mid-costal margin. No other abdominal masses were palpable.

Neurologic examination revealed a well-developed, obese, white female who was lethargic and frequently fell asleep during the examination. She was oriented to place and person, but not to time; she exhibited a marked defect in immediate recall and recent memory which was out of proportion to her other mental changes. Cranial nerve examination was normal except for large bitemporal scotomata and pallor of the optic discs. Smell was intact bilaterally. All tendon reflexes in the arms (biceps, triceps and brachioradialis) and legs (knee and ankle) were present though difficult to elicit. The remainder of the neurologic examination was within normal limits.

Radiologic examination of the chest was unremarkable; there was no significant mediastinal adenopathy. Roentgenograms of the hands revealed normal bones and no cystic lesions were seen. Radiologic examination of the skull on two occasions revealed some thickening and increased density of the cranial vault, but the pituitary fossa was not enlarged. The posterior clinoids were thought to be slightly shorter than normal. A flat film of the abdomen revealed no abnormality except enlargement of the liver.

Admission laboratory findings revealed: Hematocrit, 48; Leukocytes, 16,200; Sedimentation rate, 40 mm. per hr. (Wintrobe); Differential count: Polymorphonuclears, 71%, Band 1%, Eosinophils, 1%, Lymphocytes, 25%, Monocytes, 2%; blood urea nitrogen, 39.5 mg. per 100 ml.; FBS, 230 mg. per 100 ml.; Sodium, 144 mEq. per L.; Potassium, 3.8 mEq. per L.; Calcium, 4.8 mEq. per L.; CO_2, 27.9 mM. per L.; Cl, 103 mEq. per L.; Phosphatase, 1.0 mM. per L.; Alkaline phosphatase, 2.2 BU; T.T., 26 U; Total protein, 6.9 gm.%; Albumin, 3.5 gm.%; Globulin, 3.4 gm.%.

Initial lumbar puncture revealed clear fluid containing 20 polymorphonuclear leukocytes and 5 lymphocytes. Gram stains and Ziehl-Nielsen stains were negative. Bacteriologic cultures were likewise negative. The results of three lumbar punctures are shown below:

Date	*Protein*	*Sugar*	*Chloride*	*Pandy*	*Sediment*
8/19/56	43	88	115	+	25 poly, 5 lymph.
9/ 7/56	101	29	117	+	53 lymph. 10 polys. 2 plasma cells pellicle formed
9/ 8/56	140	32	113	Not recorded	Not recorded

An electroencephalogram revealed a diffusely abnormal pattern with bursts of 5 to 7 per sec. and 2 to 3 per sec. waves which were present in all leads, but were more marked on the right side. Electrocardiogram revealed right axis deviation with low voltage and nonspecific T-wave flattening. Air-encephalography demonstrated the interpeduncular cistern definitely tilted posteriorly. The chiasmatic cistern was not visualized. It was the radiologist's impression from this examination that there was posterior displacement of the interpeduncular cistern probably from a localized tumor mass. The clinical diagnosis of hypopituitarism with diabetes inspidus accompanied by bitemporal hemianopsia and radiologic evidence of a mass in the region of the pituitary gland prompted exploratory craniotomy.

Further investigations revealed the following: Tuberculin skin test was negative to 1st and 2nd strength P.P.D. and negative to O.T. 1:100. Radioactive iodine uptake was 16% in 24 hours and the serum protein-bound iodine was 3.2 μg%. Following surgery, thyrotropic hormone (Thytropar, Armour) in doses of 10 units I-M every 12 hours for three successive doses failed to increase the 24-hour I_{131} uptake above the control level. Cholesterol was 174 mg. per 100 ml. Basal metabolic rate was minus 7%. Urinary FSH was negative (less than 5 mouse units). Serum electrophoresis revealed: albumin 46.7%; alpha-1 globulin 7.7%; alpha-2 globulin 16.9%; beta globulin 12.8%; gamma globulin 15.8%. Urinary 17-OH-CS and 17-KS before and after a standardized 48-hour intravenous ACTH test were as follows:

Date	*Volume*	*Creatinine*	*17-OH*	*17-KS*	*Rx*
8/23/56	5980	905	1.5	5.4	—
8/24/56	5500	815	0	2.8	—
8/25/56	6200	1250	0	3.8	—
8/26/56	6060	1150	0	4.7	—
8/27/56	7700	1260	2.1	4.6	25 units ACTH
8/28/56	8600	1660	3.6	10.3	25 units ACTH

Exploration of the optic chiasm through a right frontal craniotomy under endotracheal anesthesia was performed on August 30, 1956, by Dr. Donald Matson. The arachnoid was noted to be thicker and grayer than usual, especially in the region of the optic nerves and chiasmal cistern. On the anterior aspect of the optic chiasm and above the sella as well as along the olefactory tract, there was a mass of dense vascular fibrous tissue which upon cutting had a gritty consistency. Frozen section of this material was interpreted as showing acute and chronic infiammation. The entire optic chiasm and surrounding area appeared to be involved with this granulomatous material and no effort was made to remove more than enough for microscopic study. Pathologic report of this biopsy was interpreted as granulomatous arachnoiditis consistent with sarcoidosis. Biopsy of an axillary lymph node and the atrophic skin lesions confirmed the diagnosis of sarcoidosis.

The patient was discharged on prednisone, 25 mg. twice a day, in an effort to arrest the granulomatous process which was compromising her vision. Hormonal replacement therapy also included thyroid, 100 mg. daily and pitressin tannate-in-oil in doses sufficient to regulate her diabetes insipidus. On 25 mg. of prednisone twice daily, the patient improved strikingly in strength, alertness and general well-being. However, she gradually developed marked Cushingoid features and diabetes mellitus supervened. These were controlled by a reduction in the steroid administration.

The patient required several subsequent admissions during 1956 and 1957 for evaluation of her general status and for adjustment of her medications. Her final admission on February 25, 1957, was necessitated by increasing weight gain, weakness and severe headache of 36 hours' duration. At this time there was no demonstrable improvement in her bitemporal hemianopsia nor her visual acuity. Considerable difficulty was experienced in maintaining large doses of prednisone because of the side effects of diabetes, mild hypertension and obesity. A compromise maintenance dose of 10 mg. daily was finally selected. Despite adequate diabetic, hypertensive and hormonal therapy, the patient became progressively weaker and more lethargic. She had a terminal elevation of temperature to 105.6°. Lumbar puncture revealed an elevated spinal fluid pressure of 510 mm. Shortly thereafter, the patient's temperature rose to 107.8°, and she succumbed.

XUM

Postmortem examination revealed Boeck's sarcoid with involvement of the meninges overlying the orbital gyri of the cerebral cortex and diencephalon, optic chiasm, proximal portions of the optic nerves, tuber cinereum, sphenoid sinuses, axillary, cervical, tracheobronchial and celiac lymph nodes, lungs, liver, peritoneum and vertebral bone marrow. The thyroid follicles uniformly contained abundant protein-rich colloid with acini lined by a low flattened follicular epithelium. The subcapsular stroma of the ovary formed a fibrotic eosinophilic lamina over the deeper basophilic stroma and numerous ova appear "trapped" at this junction. Within the deeper stroma were numerous recent and degenerate Graffian follicles and occasional corpora atreticum. No corpora lutea or recent corpora albicantia were seen. The adrenal glands were essentially within normal limits. The sinuses, bone, bone marrow and pars anterior of the pituitary were within normal limits (Figs. 1 and 2). The pars posterior seemed condensed and hypernuclear. Sarcoid granulomata were seen only within the diaphragm sellae and at the superior margin of the pituitary (Fig. 3). Sections of both optic nerves revealed sarcoid granulomata in and about the perineural fibrous tissue. These were associated with infiltrations of lymphocytes and plasma cells.

Examination of the brain in mid-sagittal section revealed the infundibular portion of the third ventricle from the lamina terminalis to the mammary bodies to be filled with grayish tissue. The floor and walls of the hypothalamus had lost their normal anatomical demarcations and appeared infiltrated with this abnormal tissue. The cavity of the infundibulum was greatly reduced. Proliferative tissue extended to the level of the lower border of the foramen ovale and involved the lateral portion as well as the floor of the third ventricle. The third ventricle was not otherwise abnormal nor enlarged. The sylvian aqueduct remained patent. The lateral and fourth ventricles were normal in capacity and configuration. Microscopic sections revealed sarcoidosis involving the hypothalamus (Figs. 4 and 5). The optic tracks, chiasm and leptomeninges of the base of the brain showed a severe infiltration with granulomatous tissue containing giant cells and showing a pronounced tendency to form perivascular cuffs of round cells. It is along the blood vessels that the granulomatous proliferation entered into the thalamus and the striatum.

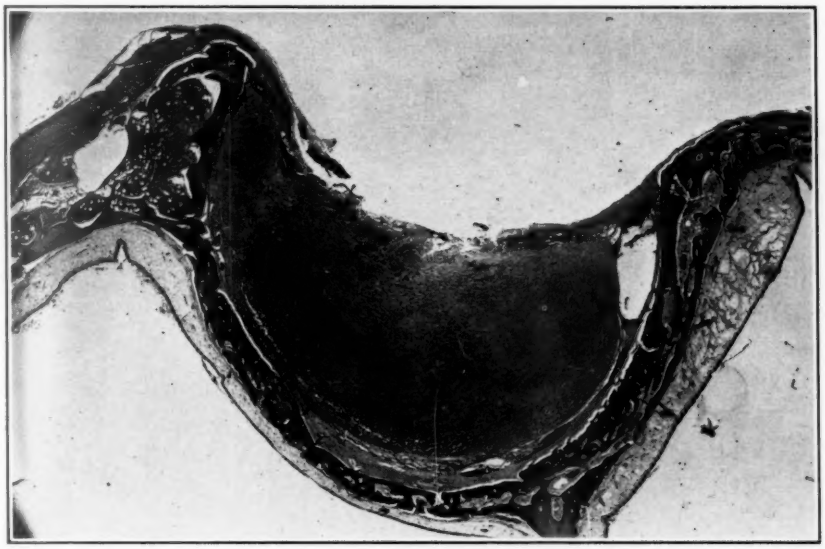

Fig. 1.—Mid-sagittal section of the sella turcica and pituitary gland under low power ($\times$ 12).

Discussion. Sarcoidosis of the base of the brain or of the pituitary gland is a rare cause of hypopituitarism. The

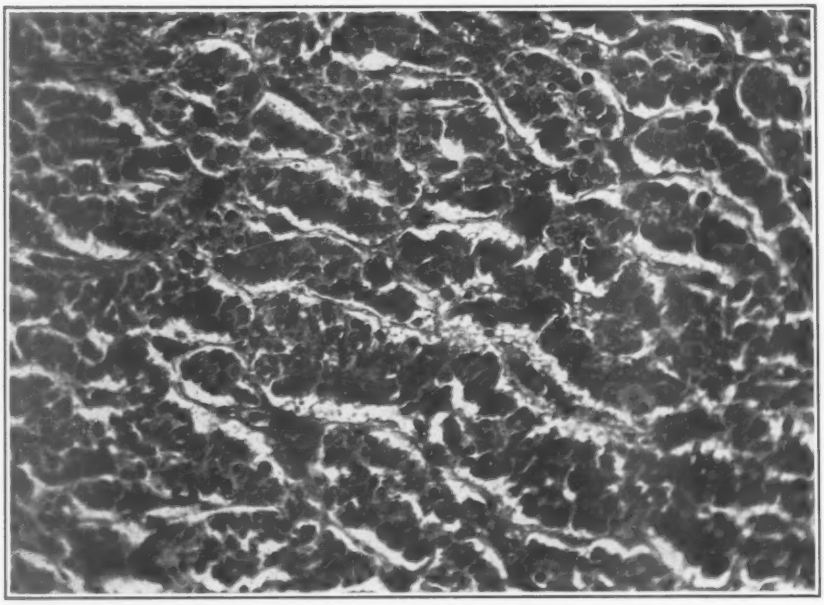

Fig. 2.—Microscopic view of a representative section of the anterior pituitary gland (× 250).

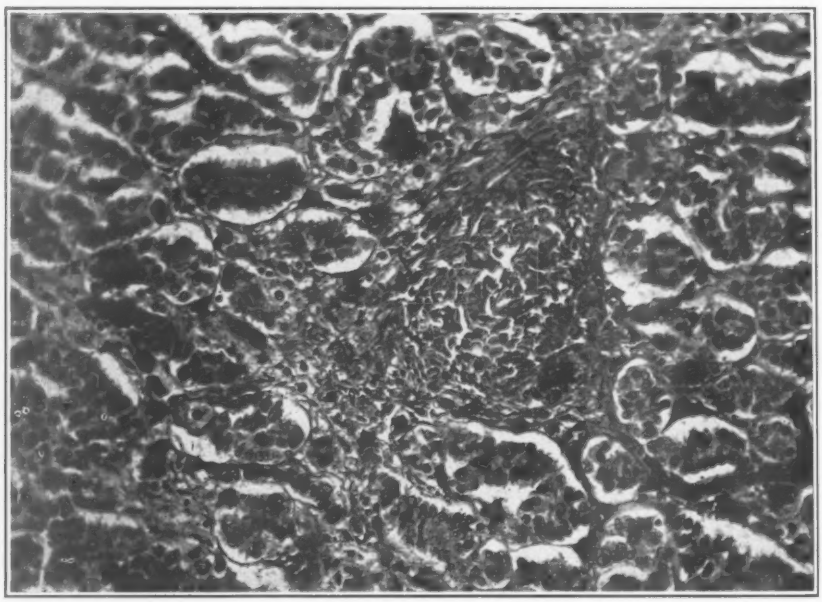

Fig. 3.—Microscopic section showing a single granulomatous lesion of the anterior pituitary gland in the region adjacent to the diaphragma sellae (× 250).

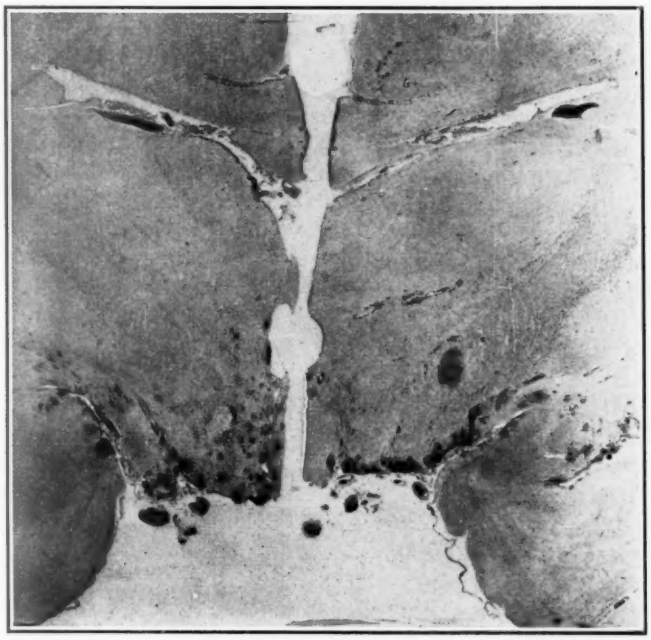

Fig. 4.—Photomicrograph under low power of the hypothalamus in the region of the pituitary gland.

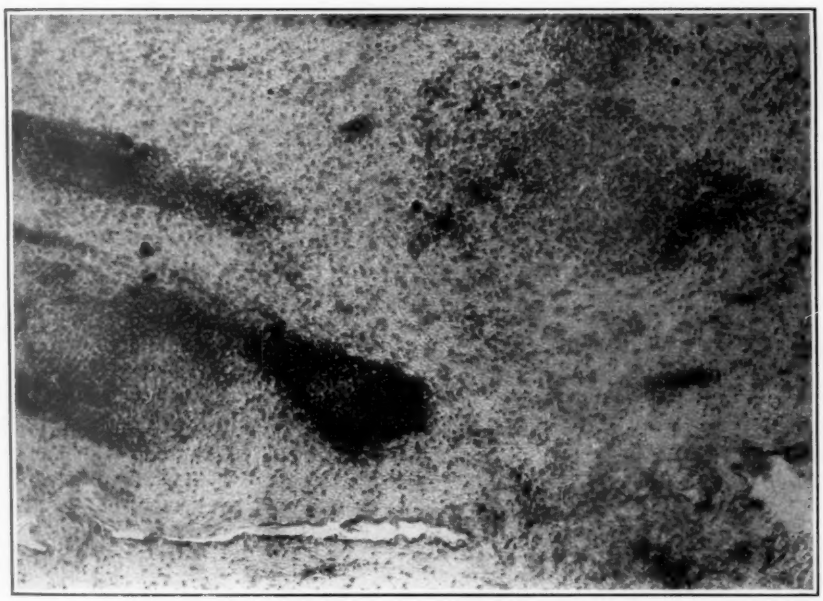

Fig. 5.—Photomicrograph under higher magnification revealing sarcoid lesions in the hypothalamus.

patient reported herein exhibited clinical features of both anterior and posterior pituitary failure which were substantiated by laboratory investigation. The most common causes of panhypopituitarism associated with a visual field defect (in this patient, bitemporal hemianopsia) are adenomas of the pituitary and craniopharyngiomas. Both of these tumors are often, but not always, associated with enlargement of the pituitary fossa; this patient had a normal size sella turcica by Roentgen ray. The diagnosis of generalized systemic sarcoidosis was originally not considered until after intracranial exploration since the only overt manifestation of systemic sarcoidosis was evidenced by the few small, atrophic lesions of the skin which were atypical for sarcoid.

Laboratory confirmation of the clinical diagnosis of pituitary insufficiency due to sarcoidosis has only rarely accompanied reports of this disorder. Indeed, conflicting evidence obtained from laboratory studies may sometimes render difficult a determination of the presence or degree of hormonal insufficiency (Van Arsdel and Williams[10]). Chronically ill patients may manifest symptoms or signs simulating those of anterior pituitary failure and, contraiwise, partial destruction of the anterior pituitary gland may occur without overt clinical or measurable laboratory evidence of hormonal insufficiency. This patient manifested pituitary failure clinically by (a) amenorrhea, (b) weakness, fatigability and coma, (c) lack of axillary, pubic and body hair, (d) dry atrophic skin with perioral wrinkling and (e) polyuria, polydipsia, and dehydration. Her skin and facial appearance also suggested hypothyroidism. Laboratory studies revealed (a) absence of urinary follicle stimulating hormone (FSH), (b) low control levels or urinary 17-hydroxycorticoids and 17-ketosteroids with only slight response to the two-day intravenous ACTH test and (c) low 24-hour I_{131} uptake and low normal serum protein-bound iodine. In this patient, thyroidal I_{131} uptake failed to respond to a total of 30 units of TSH (Thytropar).

The disclosure at necropsy of (a) an intact anterior and posterior pituitary gland, (b) colloid in the thyroid gland and (c) normal adrenal glands was unexpected in the view of the clinical and laboratory diagnosis of pituitary insufficiency. Since the major anatomic lesion which might produce hypopituitarism was in the region of the hypothalamus, it may be postulated that pituitary failure resulted from a disturbance of the hypothalamic-pituitary axis. Failure of the patient's diabetes insipidus to increase in severity upon institution of prednisone therapy suggests that anterior pituitary function was not completely abolished. Lack of increase in thyroidal I_{131} uptake following 30 units of TSH emphasizes that a negative response in this test does not necessarily indicate primary thyroid failure. The poor response to the 48-hour intravenous ACTH test is characteristic of that seen in patients with anterior pituitary failure despite the finding of pathologically normal adrenal glands. Until adequate blood and urinary assays are developed to measure normal or reduced levels of TSH, FSH, ACTH, and other pituitary hormones, the diagnosis of hypopituitarism will remain primarily a clinical diagnosis in such borderline patients. Certainly, hormonal substitution therapy should not be withheld because of insufficient laboratory confirmation of the clinical diagnosis especially where hypothalamic or pituitary lesions are thought to exist.

The diffuse inflammatory nature of this chronic granulomatous proces

obviated the possibility of any significant clinical improvement by surgical excision of the circumsellar and chiasmal lesions. Failure to alter significantly the clinical course of this patient's disease by administration of large doses of prednisone is disappointing but not unexpected (Jackson and Hood[3], Magnus[6]).

Summary. Hormonal insufficiency of the anterior and posterior portions of the pituitary gland occurs rarely as a complication of sarcoidosis. This is due to the granulomatous involvement of the pituitary gland itself.

The patient described in this report exhibited the unique occurrence of panhypopituitarism due to extensive hypothalamic involvement with sarcoidosis with a histologically intact pituitary gland. This suggests that interruption of the neural pathways between the hypothalamus and the pituitary gland is capable of producing the syndrome of both anterior and posterior pituitary failure in man. Therapeutic administration of prednisone failed to alter the clinical course of this patient's sarcoidosis.

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SUMMARIO IN INTERLINGUA

Hypopituitarismo Como Effecto de Sarcoidosis Hypothalamic

Insufficientia hormonal del portiones anterior e posterior del glandula pituitari occurre rarmente como complication de sarcoidosis. Tal insufficientia es alora le effecto de un affection granulomatose del glandula pituitari mesme.

Le patiente describite in le presente reporto exhibiva le occurrentia unic de panhypopituitarismo causate per un extense affection hypothalamic con sarcoidosis, in le presentia de un histologicamente intacte glandula pituitari. Isto pare indicar que le interruption del circuitos neural inter le hypothalamo e le glandula pituitari es capace de producer le syndrome de disfallimento pituitari tanto anterior como etiam posterior. Le administration therapeutic de prednisona non alterava le curso clinic del sarcoidosis de iste patiente.

THE CONCEPT OF PERICARDIECTOMY AS A TREATMENT FOR RECURRENT IDIOPATHIC PERICARDITIS IN THE ABSENCE OF CARDIAC CONSTRICTION*

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Surgical removal of the pericardium has long been an accepted form of treatment in patients with congestive failure secondary to pericardial constriction. Clinicians consider such surgery well-justified in view of the serious progressive disability caused by the constricting pericardial scar. Less appreciated has been the degree of disability encountered in certain patients with so-called recurrent idiopathic pericarditis. These patients show a different clinical picture largely independent of constrictive effects. Instead of constriction or tamponade, the patient develops a smoldering illness with recurrent severe chest pain, malaise, fever, and pleuritis. The end result is a pattern of disability characterized by prolonged or multiple hospitalizations, inability to work, and a state approaching total invalidism. Six patients almost totally disabled by chronic recurrent pericarditis were subjected to pericardiectomy. To date all 6 patients† have remained free of further recurrences, and have returned to good health with full activity.

Case Reports. cases 1, 2 and 3. The first 3 cases have previously been presented elsewhere (Zinsser[5]) and need not be reviewed again in detail at this time. The original 3 case reports clearly illustrated a recognizable pattern of subacute illness which at first did not seem sufficiently serious to warrant a treatment so drastic as pericardiectomy. Each separate recurrence of pericarditis tended to subside relatively promptly on symptomatic treatment and rest. However, the patients developed equally prompt exacerbations with each attempt to return to normal gainful activity. This smoldering pattern of illness was interrupted only after extensive pericardiectomy. In cases 4, 5 and 6, the recommendations for pericardiectomy were accepted relatively earlier in the course of the subacute illness than in the original cases, since a precedent of 3 cases had now been established, and the value of the procedure demonstrated to the satisfaction of a sufficient number of staff physicians.

case 4. R.J., a 20-year-old college student, noted the onset of lower right chest pain on August 24, 1957, while jogging slowly to begin conditioning himself before fall football practice. The pain was aggravated by

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†Addendum: Two additional patients have undergone pericardiectomy with equally good results since the presentation of this paper on April 28, 1958.

respiration or body movement, and became more severe over the next few days. He developed fever and was found to have both pericardial and pleural friction rubs, with an unusually loud rub over the liver. He was hospitalized elsewhere on August 29, 1957, with a diagnosis of pericarditis and pleuritis. Electrocardiograms showed changes compatible with pericarditis. He remained febrile and laboratory studies showed continued elevation of the sedimentation rate and white blood count. No etiologic diagnosis could be made despite multiple tests including several lupus preparations, a liver biopsy, skin tests for tuberculosis and fungi, and repeated studies of aspirated pleural fluid for mitotic cells, and bacterial or viral infection. He had been hospitalized for 2 months, when one of his physicians was impressed with the similarity between his case and that of the 3 cases reported before the American Clinical and Climatalogical Association on October 28, 1957. Subsequently he was transferred to the Hospital of the University of Pennsylvania on November 9, 1957, for consideration of pericardiectomy. By this time he had developed some pericardial constriction as evidenced by a venous pressure of 203 mm. of water, and a diuresis of 6 pounds of fluid after several mercurial injections.

Despite his negative tuberculin tests he was given 2 weeks of prophylactic antituberculous therapy with 1 gm. of streptomycin daily and 100 mg. of isoniazid t.i.d. On November 25, 1957, pericardiectomy was performed through a transverse sternal splitting incision. Body fluid was present between two layers of thickened pericardium. The parietal layer was easily removed, but no line of cleavage could be established between the visceral layer and the heart. This necessitated use of a cross-hatching technique with subsequent removal of small postage-stamp areas of visceral pericardium. Microscopic studies showed pericardial thickening due to increased fibrous tissue, an inflammatory exudate, and perivascular infiltration with lymphocytes and some plasma cells. The diagnosis was acute and chronic pericarditis. No known etiology could be established despite smears and cultures for bacteria or viruses. He was discharged from the hospital on December 13, 1957, and has been entirely healthy to date.

CASE 5. C.B., a 39-year-old postal clerk, first developed chest pain and fever in January, 1956. He was hospitalized for several days, and recovered without being told a definite diagnosis. Subsequently he was well until September, 1957, when he again developed a similar illness with chest pain aggravated by cough, respiration and change of position. He was hospitalized elsewhere on September 25, 1957, with fever, leukocytosis, and electrocardiographic changes leading to a diagnosis of pericarditis. With rest and antibiotics he improved and was discharged on October 5, 1957. His illness promptly recurred and he was readmitted to the same hospital on October 13, 1957. He was then continuously hospitalized for over 2 months with multiple recurrences of fever and chest pain accompanied by leukocytosis, tachycardia, prostration, and electrocardiographic changes consistent with pericarditis. A pericardial biopsy was reported as showing nonspecific pericarditis. He went home from the hospital on December 15, 1957, but remained symptom-free for only 3 days before the chest pain and fever returned. At this point, his physician discussed the case with a friend who heard the paper presented on October 28, 1957, reporting favorable results following pericardiectomy in 3 similar cases. Subsequently he was placed on prophylactic antituberculous therapy with 100 mg. of isoniazid t.i.d. and 1 gm. of streptomycin daily, and was admitted to the Hospital of the University of Pennsylvania on December 27, 1957, for possible pericardiectomy.

As in the previous cases, numerous studies failed to reveal any specific etiology for the pericarditis. Signs of pericardial constriction were absent and the venous pressure was normal on several occasions. On January 6, 1958, an extensive pericardiectomy was done through a transverse sternal incision. The pericardium was grossly thickened and adherent at numerous areas, but not constricting. Microscopic studies showed pericardial thickening due to fibrous tissue and organized fibrin. The tissue was infiltrated with lymphocytes, plasma cells and polymorphonuclear leukocytes, and was described as being vascular, with perivascular lymphocytic infiltration. The diagnosis was acute and chronic pericarditis, and no etiology could be determined pathologically or with subsequent studies for bacteria, viruses or fungi.

Postoperatively he did well and was discharged from the hospital on January 19, 1958. He has continued well to date and when last seen was working fulltime without difficulty.

CASE 6. R.E., a 49-year-old housewife, first developed chest pain early in October, 1957. The pain was severe, and was aggravated by respiration and changes in body position.

A clinical diagnosis of pleurisy was made and she recovered after a week of home treatment including several days of bedrest. In November, 1957, she had a similar illness and again recovered after a week of treatment at home. She was then well until January 14, 1958, when the pain returned in severe form, aggravated by respiration, cough and recumbency. She was comfortable only in a sitting position. When she failed to improve, she was hospitalized elsewhere on January 17, 1958. She had fever, leukocytosis, increased sedimentation rate, a loud pericardial rub, and electrocardiographic changes characteristic of pericarditis. She continued with recurrences of fever and pain, and failed to recover despite treatment including antibiotics and steroids. Since C.B. (Case 5) had been at the same hospital, her physician was aware of the favorable results following pericardiectomy in similar patients. She was then started on prophylactic antituberculous therapy with streptomycin and isoniazid in the usual doses, and was subsequently transferred to the Hospital of the University of Pennsylvania on February 9, 1958.

After admission she continued with a low-grade fever, a leukocytosis of 18,000, an active sedimentation rate, and slight reversal of the A/G ratio. There was no evidence of constriction and the venous pressure was normal. She was continued on prophylactic antituberculous treatment despite lack of evidence of tuberculosis. On February 21, 1958, her pericardium was extensively removed through a vertical sternal splitting incision. The pericardium was thickened and adherent at points, but not constrictive. Microscopic sections showed thickening by fibrosis with an inflammatory exudate consisting of lymphocytes, monocytes, neutrophils, and plasma cells.

No specific etiology for the pericarditis could be determined despite extensive studies to rule out bacterial, viral and fungal infection. Her postoperative recovery was essentially uneventful, and she has been living a normal life without recurrences of her illness to date.

CLINICAL FEATURES. The salient features of the case reports are summarized in Tables 1, 2 and 3. Chest pain was the major symptom in all patients except S.E. (Case 2). The character and distribution of chest pain was of pericardial type. The pain was located posteriorly over the shoulders and into the neck as well as anteriorly, and was aggravated by respiration, cough, rotation of the trunk, or positional changes of the body. Usually the patients had extreme discomfort in recumbency and felt better sitting up or leaning forward. All patients showed pericardial rubs at some time during their illnesses, as reported by observers of varying experience. Electrocardiograms showed RST and T changes of a type associated with pericarditis, although the changes were of minimal degree in S.E. (Case 2). Some of the electrocardiograms showed decrease in amplitude of complexes at various times. Atrial flutter was present preoperatively in one patient and occurred postoperatively in another.

All patients showed constitutional symptoms accompanying the chest pain. These included persistent low-grade fever, malaise, grippe-like sensations, and easy fatigability. Weight losses ranging up to 25 pounds occurred in some of the patients. These symptoms were accompanied by laboratory changes including a leukocytosis ranging from 10 to 20 thousand cells, increased sedimentation rate, and changes in the serum proteins with reversal of the A/G ratio in some cases.

Pleurisy was a prominent feature in all patients. Pleural friction rubs were heard in most cases, and all patients showed pleural effusions of varying degree on chest roentgenongram. The fluid obtained on pleural taps showed an increase of specific gravity and cellular content, but repeated studies were negative for mitotic cells, viruses, and tuberculosis or other bacterial infections.

Usually a clinical diagnosis of pericarditis was made based on the history, friction rub and electrocardiographic changes. Careful observation of serial chest films disclosed changes in the area of the cardiac silhouette, which

TABLE 1.—CLINICAL FEATURES*

	H. C. *1*	*S. E.* *2*	*B. S.* *3*	*R. J.* *4*	*C. B.* *5*	*R. E.* *6*
Pain	Severe	Mild	Severe	Moderate	Severe	Severe
Constitutional Symptoms	Moderate	Marked	Mild	Moderate	Marked	Moderate
Pericardial Rub	+	+	+	+	+	+
EKG Pattern	+	−	+	+	+	+
Lab. changes	+	+	+	+	+	+
Serial Roentgen-ray Changes	+					
in Cardiac Silhouette	−	+	0	+	+	+
Pleuritis with Effusion	+	+	+	+	+	+
Evidence of Constriction	0	+	0	+	0	0

*Constitutional symptoms included fever, malaise, weakness, fatigue and weight loss. Laboratory changes included leukocytosis, active sedimentation rate, anemia, and sometimes reversal of the A/G ratio.

TABLE 2.—TIME RELATIONS*

	H. C. *1*	*S. E.* *2*	*B. S.* *3*	*R. J.* *4*	*C. B.* *5*	*R. E.* *6*
Initial Attack	Oct. 1953	Feb. 1955	Sept. 1953	Aug. 1957	Jan. 1956	Oct. 1957
First Recurrence	May 1954		July 1954		Sept. 1957	Nov. 1957
Onset Smoldering Phase	Sept. 1955	Feb. 1955	May 1956	Aug. 1957	Sept. 1957	Jan. 1958
Duration Smoldering Phase (Months)	3½	11½	5½	3	4½	2
Date Operation	Dec. 1955	Jan. 1956	Oct. 1956	Nov. 1957	Jan. 1958	Feb. 1958

*Two patients seemingly entered the smoldering phase with their initial attacks, unless each had an earlier attack so mild as to be forgotten. R. E. was well for only brief periods following her initial attack and first recurrence, and it may be that her smoldering phase should be counted as starting with her initial attack in which case the duration of smoldering phase would be 3 months longer.

TABLE 3.—THE SMOLDERING PHASE*

	H. C. *1*	*S. E.* *2*	*B. S.* *3*	*R. J.* *4*	*C. B.* *5*	*R. E.* *6*	*Total*
Duration in Months	3½	11½	5½	3	4½	2	30
Number of Hospitalizations during Smoldering Phase	3	4	4	2	3	2	18
Time in Hospital (%)	75	20	52	98	90	100	55
Sustained Work (%)	0	33	0	0	0	0	13

*This table documents the misery and disability of these patients during the smoldering phase. The 6 patients were chronically ill for a total of almost 30 months. They were hospitalized 18 times, and spent a total of 475 out of 870 days in the hospital or about 55% of the smoldering period. Only one was capable of any sustained work, and that by superhuman effort on his part. We have omitted a table which documented the cost of hospitalizations and the weight or thickness of hospital charts.

was a helpful diagnostic finding in most cases. In one patient angiocardiography was used to demonstrate the unopacified area external to the cardiac chambers, which is accepted as presumptive evidence of pericarditis, particularly when present along the right atrial border. In one patient a pericardial biopsy had been done elsewhere to confirm the diagnosis. Three patients had been subjected to pericardial taps, which in general proved unrewarding and which we personally do not favor in this group of patients.

It is important to emphasize the prolonged nature of the disability in these patients. Physicians not familiar with this problem tend to underestimate the degree of handicap, since the patient becomes reasonably comfortable and the process seems to subside quickly with enforced bedrest. Unfortunately, the patients are unable to return to normal life or undertake even modest activity without the process re-igniting, generally within a few days following discharge from the hospital. Physical activity seems to represent the major factor in causing recurrences, which can flare up despite continuation of other treatments such as antibiotics (all cases), antituberculous therapy (all cases), and steroids (2 cases). In this group of patients, pericardiectomy has been a last resort when the process has failed to subside after repeated trials of medical treatment. Table 3 attempts to "document the misery" of the smoldering phase of the illness in these patients. One would not be concerned with the earlier attacks which subsided on conservative treatment and permitted the patient to return to normal activity or gainful occupation for months or years. Rather the indication for pericardiectomy has been the development of the smoldering phase, with persistent or recurrent pain and fever, which produced almost continuous disability terminated only by operation. Aside from strictly medical aspects of the problem, this causes a tremendous economic burden which has practically pauperized certain of the patients during the long periods of high expense and no income.

Discussion. The overall trend in pericardial surgery has been in the direction of earlier operation ever since the advent of streptomycin. Prior to that time, early surgery was hazardous due to the possibility of invading an unrecognized tuberculous infection and causing uncontrolled spread of the disease. Since tuberculosis was suspected as the etiologic factor in most cases of constrictive pericarditis, one hesitated to attempt surgery until the disease process was presumably no longer active. In 1951, Holman and Willett[1] first suggested the desirability of early surgery in patients with proven tuberculosis. Actually the 4 cases they reported had developed an advanced state of cardiac impairment prior to surgery; however, they clearly recognized in retrospect the desirability of earlier surgery and pointed out the expected technical advantages of easy dissection during the stage of effusion, as opposed to the difficulty encountered later when operation was delayed until the pericardium and myocardium were intimately adherent. This concept of early surgery in patients with proven tuberculosis has seemed quite sound. Furthermore, for a number of years we have considered it equally logical to recommend early surgery in patients with pericardial effusion even in the absence of proven tuberculosis. For one thing, some patients with pericardial effusion of unknown etiology actually have tuberculosis despite early lack of proof, and ultimately follow a course similar to other proven tuberculous cases. In addition, experience

suggests that patients with other types of idiopathic pericardial effusion can develop constrictive pericarditis, and subsequent studies fail to reveal any specific etiology either on microscopic sections or cultures of surgical material. Others have also adopted this approach of early surgery, although we agree with those who favor extensive pericardiectomy (Mannix and Dennis[2], Shumacker and Harris[4]) rather than those who advocate button biopsy (Proudfit and Effler[3]). Biopsy seems less likely to prevent ultimate constriction by the large unremoved area of diseased pericardium, and certainly failed to halt the smoldering disease process in one of our patients (Case 5).

This background indicates a general trend toward earlier surgery, particularly in patients with proven tuberculosis where prevention of ultimate constriction seems important. The present cases illustrate a form of disability due to pericarditis, entirely separate from the older recognized difficulties of constriction or tamponade. The patients showed primarily a febrile illness characterized by pain, constitutional symptoms, and laboratory evidence of pericarditis and pleuritis. This smoldering illness failed to subside despite months of medical treatment, and the patients were virtually invalids with all the superimposed economic implications of invalidism. Surgery was recommended primarily to interrupt this process rather than on the basis of treating or preventing pericardial constriction or tamponade. In 2 patients, signs of congestive failure did develop prior to their final acceptance of the recommended pericardiectomy. This suggests that prevention of future constriction does represent a byproduct of operation in this group of patients, although the pericardiectomy was intended primarily to end the long, smoldering, painful, febrile illness. Perhaps this group of patients with continued long-smoldering pericarditis may be more likely to develop ultimate constriction than patients with occasional self-limited recurrences of pericarditis.

The decision as to when operation becomes indicated in these patients is difficult. Most patients with idiopathic pericarditis recover satisfactorily after single episodes or even several widely-spaced recurrences. Surgery would not be recommended for these patients who recover promptly, but only for those who develop a smoldering illness of the type described in the case reports. Such cases are not numerous, as testified by the small number encountered since the first patient was operated on in 1955. In addition to those sent to surgery, several other patients are being followed who potentially represent candidates for pericardiectomy; as yet their degree of disability has not warranted operation.*

Multiple studies before and after operation have failed to disclose any specific etiology for the pericarditis. Skin tests, agglutinations, lupus preparations, and cultures of pleural fluid, pericardial fluid or tissue removed at operation have failed to provide any evidence for a definite diagnosis of collagen disease or specific infection of fungal, viral, or bacterial origin. Microscopic sections showed only nonspecific changes which were of fairly consistent type, with pericardial thickening due to fibrosis, infiltration by both chronic and acute inflammatory cells, and increased vascularity with perivascular lymphocytic infiltration. While the second strength tuberculin test was positive in all but one patient, no evidence of tuberculosis could be found on the microscopic sections or by culture in any patient. Despite absence of preoperative evidence for tuberculosis, it was considered imperative to give all patients antituberculous treatment pro-

*Two of these have since undergone operation with good results.

phylactically before operation, and it was continued arbitrarily for several months postoperatively in all but one patient. This precaution was considered essential preoperatively, because of the notorious difficulty of obtaining definite proof of tuberculosis, and the equally well-known hazards of surgery in untreated active tuberculous pericarditis.

A brief discussion of the place of steroids in the treatment of smoldering idiopathic pericarditis seems worthwhile, since this question has invariably been raised in the discussion period following previous presentations of the material (Zinsser[5,6]). Entirely aside from any potentially favorable effects of surgery in preventing pericardial constriction, we have favored pericardiectomy as the treatment of choice for three main reasons. First, steroids had been administered unsuccessfully to 2 of the 6 patients who subsequently were "cured" following pericardiectomy. Second, we have hesitated to use steroids in a situation where tuberculosis might possibly be present despite failure to obtain bacteriologic proof even on multiple studies. Third, commitment to long-term steroid therapy seems undesirable when another course of treatment is available. In good hands, pericardiectomy probably carries less risk over all than long-term steroid administration with its worrisome side-effects, including potassium depletion, fluid retention, decreased resistance to infection, possible ulcerogenic effect, or the later withdrawal hazards of adrenal collapse during periods of stress such as trauma, anesthesia or surgery.

The exact mechanism by which pericardiectomy successfully terminated the smoldering febrile illnesses of these patients is not clear. In a vague way one might suspect that excision of considerable diseased tissue in some way removed a "focus of infection," although this explanation has not been entirely satisfactory. Barring a better explanation, we have assumed that the pericardium must be removed as extensively as possible. Creation of a button biopsy elsewhere had failed to help one patient who subsequently was restored to health after extensive pericardiectomy. A sternal-splitting technique has been employed to obtain the exposure necessary for as complete removal of the pericardium as possible. Anything less might conceivably fail to end the long-term disability in these patients.

Summary and Conclusions. 1. Pericarditis can produce a form of disability entirely separate from pericardial constriction or tamponade. 2. Six patients with idiopathic pericarditis have shown a smoldering febrile illness characterized by recurrent severe chest pain, with constitutional symptoms and pleuritis. 3. These patients failed to respond to standard treatment, and developed long-term disability with multiple hospitalizations, inability to work and a state approaching total invalidism. 4. All 6 patients were subjected to pericardiectomy and were restored to complete health with no further recurrences of their illness to date.

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(Interlingua on page 476)

A PATIENT WITH RIGID SPINE (RHEUMATOID ARTHRITIS), AORTIC VALVULAR STENOSIS AND ATRIO-VENTRICULAR NODAL AND RIGHT BUNDLE BRANCH BLOCK*

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A number of recent reports have stressed the association of rheumatoid arthritis and heart disease, the association being particularly frequent in patients with rheumatoid ankylosing spondylitis (Ansell, Bywaters and Doniach[1], Bauer, Clark and Kulka[2] Clark and Bauer[7], Schilder, Harvey and Hufnagle[14], Toone, Pierce and Hennigar[18]). A common triad is (1) rheumatoid ankylosing spondylitis, (2) inflammation of the aortic valve and scarring of the pericardium, and (3) conduction defect (atrio-ventricular nodal or bundle branch block, or both). One of the most common clinical findings is aortic valvular insufficiency and stenosis (Ansell, Bywaters and Doniach[1], Bauer, Clark and Kulka[2], Clark and Bauer[7], Clinico-pathological Conference[9], Schilder, Harvey and Hufnagle[14], Sokoloff[16], Toone, Pierce and Hennigar[18]). The following patient is presented as an example of rheumatoid spondylitis associated with aortic stenosis and atrio-ventricular nodal and right bundle branch conduction defects with a brief review of the literature.

Case Report. The patient, a 53-year-old white male college professor, was studied at Tulane Medical School in November, 1958. He was well until 23 years ago when he first noted recurrent back pain. There were remissions in pain as his spine gradually stiffened with the final development of kyphosis and a fixed spine. At various times the peripheral joints were involved. A diagnosis of rheumatoid spondylitis was made and in recent years the patient has been treated intermittently with adrenal corticosteroids. At present, his back pain is usually precipitated by fatigue or over-exertion.

In August, 1958, he noted easy fatigability and 6 weeks later developed giddiness and dyspnea while climbing three flights of stairs. He more recently experienced giddiness when standing suddenly. He counted his radial pulse and found it to vary between 36 and 60 beats per minute. Serial electrocardiograms dating back to 1947 have shown a gradual development of right bundle branch block.

The patient had "growing pains" in early adolescence. Eleven years ago he had a pneumonitis from which he recovered uneventfully, 6 years ago he passed a renal stone, and 9 months ago he underwent cholecystectomy for symptomatic cholelithiasis. He was never told that he had a heart murmur, a cardiac lesion or rheumatic fever.

Physical examination revealed a height of 72½ inches, a weight of 211 pounds, blood pressure of 150/62 mm. Hg, and a pulse rate of 40 beats per minute. A kyphosis was present with definite limitation of motion in all segments of the spine. Examination of the heart revealed no clinical enlargement. There was no pulse deficit. A

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loud, harsh, systolic murmur was heard over the precordium but maximally at the base and it was transmitted into the neck. It began with the first sound but was not diamond shaped. The remainder of the physical examination was grossly normal.

Routine laboratory data were normal. Cardiac fluoroscopy revealed a normal sized heart with calcification of the aortic valve.

Fig. 1.—Antero-posterior view of lumbar spine showing ankylosis of the "bamboo-tree" type.

Teleroentgenogram of the heart was normal. Roentgenograms of the cervical, dorsal and lumbosacral spine showed an ankylosing spondylitis of the "bamboo-tree" type (Fig. 1). An electrocardiogram showed a 2:1 atrioventricular block with complete right bundle branch block (Fig. 2).

A diagnosis of rheumatoid spondylitis associated with aortic stenosis, a high degree of atrio-ventricular block and complete right bundle branch block was made.

COMMENT. The evidence seems to be increasing in support of heart disease in association with rheumatoid arthritis. Dunham and Kantz[11] in a review of 20 cases of rheumatoid spondylitis indicated the association with pericarditis in some patients. Herrick and Tyson[13] in a discussion of rheumatoid spondylitis presented 10 patients and referred to the association of endocarditis in some patients. They were of the opinion that the endocarditis

was indistinguishable from that seen in rheumatic fever.

In an extensive review of the literature on "rheumatism" Bywaters[6] felt that three primary points of view existed: (1) rheumatic fever and rheumatoid arthritis are closely allied if not the same disease, (2) rheumatic fever and rheumatoid arthritis are different but may occur in the same patient, and (3) rheumatic fever and rheumatoid arthritis are different, but certain types of rheumatic fever may progress to a chronic form of arthritis (Jaccoud's sign) distinguishable with difficulty from rheumatoid arthritis, and rheumatoid arthritis can produce a carditis distinguishable with difficulty from that following rheumatic fever. In his own series of 27 patients with rheumatoid arthritis 8 had heart disease. A detailed anatomical study of these 8 patients revealed 3 admittedly small groups (1) those with rheumatoid arthritis and

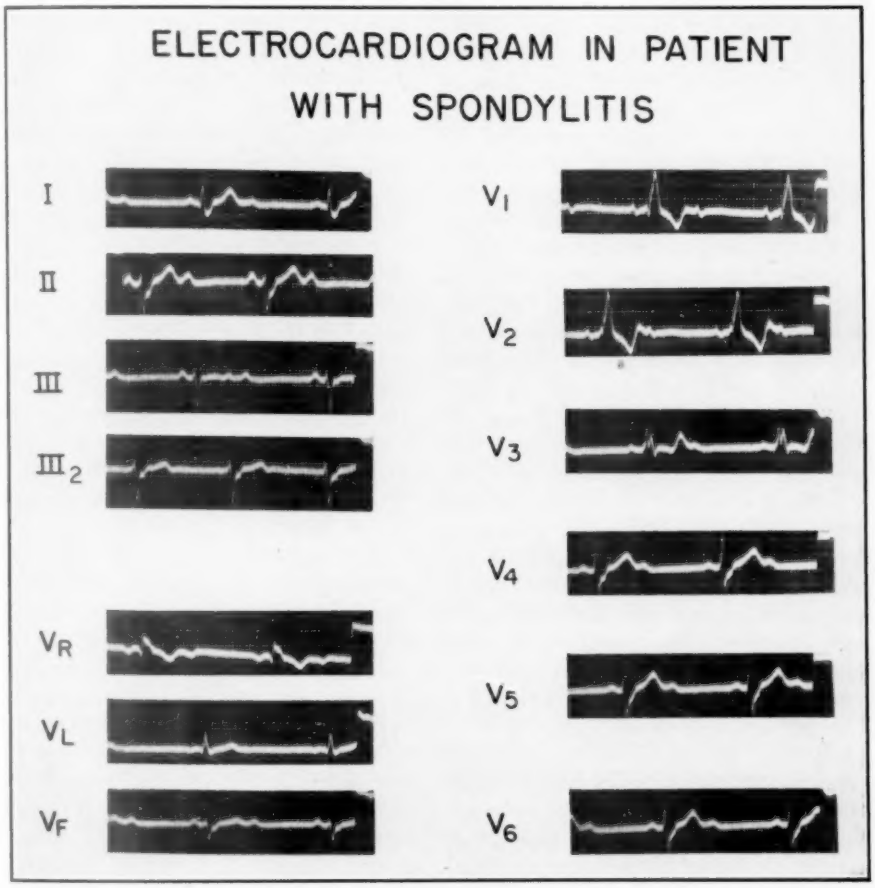

Fig. 2.—Electrocardiogram showing 2:1 atrioventricular block and complete right bundle branch block.

carditis, (2) those with rheumatic heart disease who later developed rheumatoid arthritis, and (3) those with rheumatic fever and carditis who progressed to a chronic arthritis distinct from rheumatoid arthritis. Bywaters was of the opinion that the third point of view indicated above was the correct explanation for these 8 patients.

That rheumatic fever can progress to a chronic form of disabling arthritis is supported by the studies of Sharp[15] and Thomas[17]. Thomas described 29 cases with recurrent acute polyarthritis, valvulitis and variable joint deformities, which he felt probably represented recurrent rheumatic fever. He stated, however, that the association between rheumatic fever, ankylosing spondylitis and rheumatoid arthritis is unclear. There were no necropsies in his series, but 10 of the 12 patients with spondylitis were males, and few of these had peripheral joint deformities although they had recurrent episodes of acute arthritis and almost all had mitral and aortic valvulitis clinically. Schilder, Harvey and Hufnagle[14] described the murmurs of aortic and mitral valve disease but concluded that the apical diastolic rumbling murmurs were Austin-Flint murmurs; minimal involvement of the mitral valve was found at necropsy.

Sokoloff[16] reviewed 101 necropsies of patients with rheumatoid arthritis from a cardiac point of view. He discussed the many sources of error which may account for some of the present differences of opinion. However, after eliminating all the complicating factors, he still had a group of patients in which heart disease appeared to be a manifestation of the rheumatoid process. None of his 17 patients with rheumatoid spondylitis had heart lesions. Toone, Pierce and Hennigar[18] studied 265 cases of rheumatoid spondylitis including 2 with postmortem examinations and found 8 with aortitis and aortic regurgitation attributed to the rheumatoid process.

In 1954, Gleckler[12] described a 42-year-old man who developed acute carditis during an acute exacerbation of his rheumatoid arthritis. The carditis subsided completely after a few weeks of therapy but the arthritis progressed to an ankylosing spondylitis. In the same year, Bevan *et al.*[4] reported 2 patients with pancarditis, pleuritis, synovitis and granulomatous lesions in the kidneys and lungs which progressed to fatal termination. In these 2 patients the granulomatous lesions were indistinguishable from those previously described by other authors as characteristic of the subcutaneous nodules found in rheumatoid arthritis.

The particular association of rheumatoid spondylitis with aortic valvular lesions has been emphasized (Bauer, Clark and Kulka[2], Clark, Kulka and Bauer[8], Toone, Pierce and Hennigar[18]). These reports indicated the predilection of rheumatoid spondylitis for males and its association with aortic insufficiency. They further described a focal destruction of the elastic tissue in the aortic ring and base of the aorta causing dilatation. The aortic cusps became scarred and retracted with rolling of the edges and were often calcified. This endocarditis often progressed to involve the anterior cusp of the mitral valve. In none of these reported cases were Aschoff's bodies found.

Clinically, the patients usually have aortic insufficiency but may have aortic stenosis and mitral stenosis as well. Angina pectoris is a common complaint. Ansell, Bywaters and Doniach[1], Bernstein and Broch[3] and Schilder, Harvey and Hufnagle[14] described patients showing this combination. Two more such patients were described in clinicopathological conferences[9,10]. The aorti-

tis and valvulitis are very similar to that seen in syphilis but none of the patients described had a history of lues and repeated serological and treponema immobilization tests were negative. In all reports, emphasis was placed on the fact that the cardiac lesion often develops during an acute exacerbation and usually occurs late in the course of the disease. Blumberg and Ragan[5] felt, after reviewing 311 cases of rheumatoid spondylitis, that its association with heart disease may be fortuitous but admitted that the problem needed clarification.

The patient described in this report developed rheumatoid arthritis at the age of 30 years. Twelve years later electrocardiographic evidence of heart disease was first noted but it was not until 23 years after the onset of the illness that clinical evidence of heart disease developed. The presence of rheumatic fever might be suggested by the history of "growing pains" in early adolescence, but the time lapse of 40 years before heart disease became apparent, and the fact that no heart murmurs were noted in the past, makes rheumatic fever unlikely. The question of arteriosclerotic heart disease might also be raised but the lack of evidence of arteriosclerosis elsewhere in the body, and the severe degree of valvulitis, tend to eliminate this as the etiologic factor.

It is our impression that the patient described above represents another instance of rheumatoid ankylosing spondylitis with a rigid spine in association with aortic stenosis and atrio-ventricular nodal and right bundle branch conduction defects resulting from the rheumatoid process. The clinical syndrome needs careful consideration to learn more about prognosis, clinical course, prevention, extent, if any, of a myocardial damage, and aspects of treatment.

Summary. A patient with rheumatoid ankylosing spondylitis and rigid spine in association with aortic stenosis and atrio-ventricular nodal and right bundle branch blocks is presented. The literature describing the association of rheumatoid arthritis, particularly rheumatoid spondylitis, with heart disease has been briefly reviewed. The syndrome needs careful study to evaluate cause, course and management of the disease.

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SUMMARIO IN INTERLINGUA

Un Patiente con Rigiditate del Spina Dorsal (Arthritis Rheumatoide), Stenosis de Valvula Aortic, e Bloco de Nodo Atrio-Ventricular e de Branca Dextere

Es presentate le caso de un patiente con rheumatoide spondylitis ankylosante e rigiditate del spina dorsal in association con stenosis aortic e blocos del nodo atrio-ventricular e del branca dextere. Es presentate un breve revista del litteratura concernite con le association de arthritis rheumatoide, specialmente spondylitis rheumatoide, e morbo cardiac. Le syndrome demanda un studio meticulose pro le evalutation del causa, del curso, e del tractamento.

SUMMARIO IN INTERLINGUA

(See page 464 for original article)

Le Conception de Pericardiectomia Como Therapia de Recurrente Pericarditis Idiopathic in le Absentia de Constriction Cardiac

1. Pericarditis pote producer un forma de invaliditate que ha nihil a facer con constriction o tamponage pericardial.

2. Sex patientes con pericarditis idiopathic monstrava un somnolente forma de morbo febril, characterisate per le recurrentia de sever grados de dolor thoracic, con symptomas constitutional e pleuritis.

3. Iste patientes non respondeva al tractamento standard. Illes disveloppava un prolongate incapacitate con multiple hospitalisationes, le impossibilitate de travaliar, e un stato non multo differente ab invaliditate total.

4. Omne le 6 patientes esseva subjicite a pericardiectomia. Per iste mesura illes esseva restaurate a un stato de bon valetude, sin recurrentias del morbo usque al tempore presente.

THE MYOCARDIAL METABOLISM OF FRUCTOSE*

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PROFESSOR OF MEDICINE

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The normal myocardium has the ability to utilize a wide variety of foodstuffs, the actual usage of a given substrate depending to a large extent on its availability (Bing[3]). Carbohydrates, especially glucose and lactate, supply an important part of the heart's energy requirements (Bing *et al.*[3,5]), although in the postabsorptive state the heart derives the major part of its energy supply from fatty acids. In diabetics, the myocardial uptake of glucose is relatively diminished in the presence of high arterial glucose concentrations (Ungar *et al.*[25]). The hexose fructose enters into the metabolic pool even more rapidly than glucose, when given intravenously (Weichselbaum, Elman and Lund[26]). Its uptake is unimpaired in diabetics (Miller *et al.*[17,18], Smith, Ettinger and Seligson[23]).In view of these findings, a study was undertaken to determine whether the myocardium extracts significant quantities of fructose and whether fructose affects the myocardial utilization of other substrates.

Material and Methods. DETERMINATIONS ON HUMANS. Eleven patients are included in this study. Their ages range from 24 to 45 years. All are male. Two (H.A. and L.M.) are diabetics, controlled on daily doses of 35 to 40 units of NPH insulin respectively. Neither had known heart disease. At the end of a complete workup the cardiac diagnoses of the other 9 patients were as follows: no heart disease could be detected in two; 3 suffered from mitral stenosis; one had aortic insufficiency; one had recent pericarditis; 2 were in congestive heart failure for which no adequate explanation has been found. Right heart catheterization was carried out in a routine manner. All patients were in a fasting state. The two diabetics received no insulin the morning of the procedure. Under fluoroscopic control, the tip of a Birdseye catheter was placed in the coronary sinus (Bing *et al.*[6]). Arterial blood was obtained through an indwelling needle in the brachial or the femoral artery. Coronary blood flow was obtained by the nitrous oxide desaturation method (Bing *et al.*[4]) in 6 of the normal patients and in both of the diabetics. The determination of coronary blood flow was carried out prior to the infusion of fructose. A second determination during the infusion of fructose was not performed, since previous work had indicated that the coronary blood flow as determined with nitrous oxide does not change appreciably during brief periods of observations (Ballard, Danforth and Bing[1]). Arterial and coronary sinus samples for fructose, glucose, pyruvate, lactate, and ketones were obtained simultaneously. Each result represented the average of two consecutive blood samples. After baseline blood samples had been collected, 10% fructose in saline was infused intravenously.

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TABLE 1.—ARTERIAL LEVELS AND ARTERIAL-CORONARY SINUS DIFFERENCES

Patient		Priming Dose (gm.)	Duration Priming Dose (min.)	Fructose (mg./100 ml.)		Glucose (mg./100 ml.)		Pyruvate (mg./100 ml.)		Lactate (mg./100 ml.)		Ketones (mg./100 ml.)	
				Arterial	Δ	Arterial	Δ	Arterial	Δ	Arterial	Δ	Arterial	Δ
JW	a	10	15	0	0	112.3	12.8	0.71	0.023	13.5	6.67	1.50	0.85
	b			20.7	−9.4	131.7	10.6	1.71	0.49	28.7	5.6	1.88	0.31
	c			28.0	−3.9	119.6	7.3	0.98	0.32	23.7	8.95	1.99	0.37
GH	a	20	10	0	0	94.2	3.4	0.47	0.29	8.40	1.2	3.79	0.60
	b			85	9	118.2	13.5	0.35	0.09	21.5	2.8	2.04	0.42
	c			79.9	3.2	110.8	5.1	0.44	0.13	23.4	2.9	1.72	0.19
RD	a	30	12	0	0	79.5	5.6	0.344	0.002	8.67	5.42	0.99	0.15
	b			56	−1.9	98.4	2.9	0.736	0.287	28.9	11.05	1.72	0.56
FE	a	20	10	0	0	87.2	4.8	0.61	0.22	6.89	1.26	3.06	0.68
	b			83	6.0	132.0	10.0	0.92	0.42	26.48	9.44	2.56	0.48
	c			72	6.8	128.6	5.2	1.01	0.42	24.58	7.94	3.01	0.36
EP	a	15	10	0	0	91.4	5.7	0.55	0.16	4.78	3.19	2.69	1.02
	b			97.5	−0.8	124.2	7.4	1.30	0.72	29.0	11.10	2.85	0.54
JS	a	20	10	0	0	67	0	0.63	0.07	5.90	1.99	2.17	0.66
	b			112.5	−0.3	76.1	10.6	1.07	0.35	19.62	6.21	3.11	0.80
	c			90.7	−1.4	105.1	11.8	1.70	0.90	24.88	6.00	3.14	0.97
MR	a	40	18	0	0	82.8	18.9	0.54	0.18	7.55	4.13	1.24	0.49
	b			120.6	−0.6	119.7	22.2	0.90	0.17	30.11	11.82	1.74	0.27
	c			97.2	−2.0	113.6	18.2	0.84	0.16	28.2	12.3	1.47	0.13
ES	a	14	14	0	0	79.1	6.5	0.64	0.20	4.93	0.89	2.61	0.79
	b			77.5	2.1	84.7	2.4	2.42	1.40	25.8	7.96	2.47	0.20
	c			80.4	1.2	93.1	1.7	2.94	1.92	25.06	6.10	1.89	0.29
BW	a	24	10	0	0	90.45	2.2	0.72	0.19	5.24	1.00	0.93	0.39
	b			117.1	8.8	129.4	0.7	2.37	1.19	23.3	7.88	1.79	0.17
	c			101.6	7.4	135.0	4.1	2.28	1.29	24.59	8.25	1.53	0.15
Mean	(a)			0	0	85.2	6.66	0.567	0.148	7.32	2.86	2.12	0.625
Mean	(b)			85.5	1.43	112.7	8.92	1.308	0.568	25.92	8.21	2.24	0.417
Mean	(c)			78.5	2.56	115.1	7.63	1.455	0.734	24.91	7.48	2.11	0.351
						Diabetic Patients							
HA	a	22.5	13	0	0	207	−3.0	0.46	0.16	7.51	1.08	6.92	2.14
	b			69.7	−1.9	259	6.5	0.54	0.14	21.10	1.15	6.91	0.99
	c			92.3	2.8	295	16.5	0.46	0.04	18.77	0.93	8.76	1.77
LM	a	17.5	6	0	0	236.5	16.0	1.22	0.31	5.78	0.42	10.05	4.69
	b			41.4	−0.6	293	18.5	1.12	0.003	15.49	0.51	8.40	1.75
	c			41.9	−2.1	309	16	1.09	0.12	13.07	0.61	7.39	2.46

Δ represents coronary arteriovenous difference.

A priming dose of fructose, varying between 15 and 40 gm., was administered. In order to insure as much as possible a steady state during infusion and to avoid effects of changes in fructose concentration on substrate extraction by the heart, the time interval between priming dose and first sampling was usually more than 6 minutes. The constant infusion was maintained throughout the rest of the procedure. In most cases sampling was carried out twice during the course of the infusion. (Samples B and C, Table 1.)

deviation from the normal myocardial extraction of foodstuffs in patients with heart disease, whether compensated or in failure (Blain *et al.*[7]).

ANIMAL EXPERIMENTS. Six dogs were anesthetized with intravenous pentobarbital (30 mg. per kg. weight). Thirty to 40 mg. of heparin were given intravenously as an anticoagulant. A Birdseye cardiac catheter was introduced into one of the external jugular veins. Under fluoroscopic control, the catheter was guided into the coronary sinus and

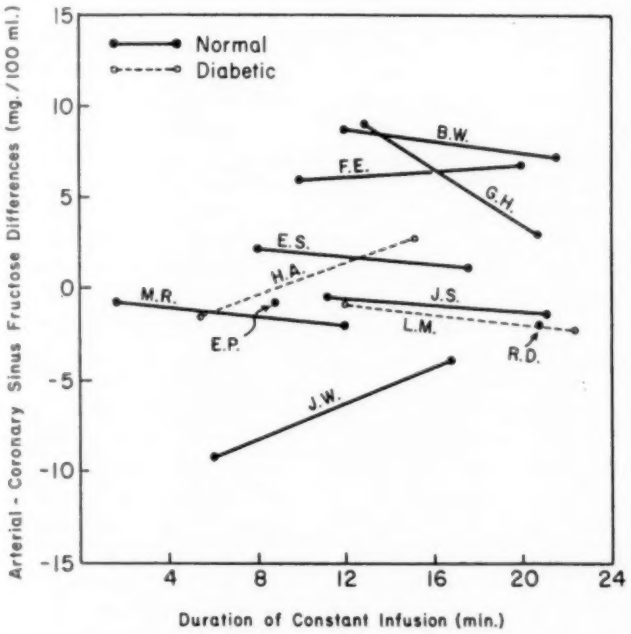

Fig. 1.—Arterial-coronary sinus fructose differences obtained during course of constant intravenous infusion of fructose in man.

Blood fructose was determined by the method of Weichselbaum, Margraf, and Elman[27]. In this laboratory the recovery of quantities of fructose of from 40 to 80 μg. ranged from 92.5 to 96%. The final results were corrected according to the reading of the standard. Blood glucose was obtained by the enzymatic method of Teller[24]. Pyruvate values were determined by the method of Friedemann and Haugen[8] using a trichloracetic acid filtrate. Lactate was measured according to Barker and Summerson[2] and ketones according to Greenberg and Lester[9].

All data from nondiabetic patients are grouped together since one would expect no

left in place. Another catheter was placed in the femoral artery. Following the collection of control arterial and coronary sinus blood samples, a constant infusion of 10% fructose in saline was started in the veins of a foreleg at a rate calculated to deliver 0.5 gm. per kg. body weight in 30 minutes. Paired arterial and coronary sinus blood samples were obtained after 15 and 30 minutes of infusion. The fructose was then discontinued. Two more paired samples were collected 5 and 30 minutes later.

Results. BLOOD FRUCTOSE LEVELS. Initial arterial and coronary sinus levels

of fructose were zero. Arterial fructose levels rose quickly during the infusion. The arterial fructose level rose slightly between the two samplings in 4 patients and fell in 5 of them. In one patient the level remained essentially unchanged.

MYOCARDIAL FRUCTOSE EXTRACTION. The coronary arteriovenous differences of fructose are illustrated in Table 1 and Fig. 1. It may be seen that these range from −9.4 to +8.8 mg. per 100 ml., with averages of 1.4 and 2.5 mg. per 100 ml. for the two samples respectively. The coronary sinus fructose concentration greatly exceeded that in arterial blood in patient J.W. (Table 1, Fig. 1). The fructose difference in this patient across the myocardium had returned close to zero 18 minutes after the priming dose. Two patients (F.E. and B.W., Fig. 1, Table 1) had a significant myocardial uptake in two samples. The patients showing large positive and negative balance across the myocardium did not differ from the rest of the patients or from each other in regard to the size of the priming dose, rate of infusion, the relationship of priming dose to the rate of infusion, or the time of sampling.

CHANGES IN GLUCOSE AND INTERMEDIARY METABOLITES. Arterial glucose rose in all patients. The rise varied considerably from patient to patient. In the normal group the minimum rise was from 79 to 84.7 mg. per 100 ml., and the maximum from 87 to 132 mg. per 100 ml. (Table 1). Higher fructose levels were not necessarily correlated with higher levels of blood glucose. The blood lactate rose in every case (Table 1). It reached a plateau early as evidenced by the fact that there was no consistent rise in lactate between the drawing of subsequent samples. In fact, the mean arterial concentration fell slightly. Blood pyruvate levels also rose in the majority of patients. Again there was no consistent rise between the sampling. Blood pyruvate levels did not rise in the diabetics. Ketones rose slightly in 6 and fell in 3 of the normals (Table 1). In the diabetics, the initial ketone levels were considerably higher than in the normals (6.92 and 10.0 mg. per 100 ml.) in contrast to the mean normal of 2.12 mg. per 100 ml.(Table 1). The ketones rose slightly in one diabetic and fell in the other.

MYOCARDIAL SUBSTRATE EXTRACTION. In 5 of the nondiabetic individuals a rise in arterial glucose concentration was associated with an increased coronary A–V glucose difference (Table 1). In 3 patients there was a decrease in the coronary A–V difference, and in one, both an increase and a decrease were found at different times during the fructose infusion. In the 2 diabetics, the myocardial A–V glucose difference increased; in one, the increase was considerable, in the other, minimal (Table 1). Similar to results previously published from this laboratory, the myocardial extraction of glucose was below what one would have predicted in a normal with comparable arterial glucose concentrations (Ungar *et al.*[25]). The coronary A–V differences in the diabetic for lactate and pyruvate were less than the normal mean. In the normals, increases in levels of arterial lactate or pyruvate were paralleled by greater coronary A–V differences of these substrates. Such was not the case in diabetics. The myocardial arteriovenous ketone differences fell in the normals from a mean of 0.625 to a mean of 0.417 mg. per 100 ml. in spite of a rise in mean arterial levels of from 2.12 to 2.24 mg. per 100 ml. (Table 1).

ANIMAL EXPERIMENTS. The results are presented in Table 3. Most of the dogs showed a slight positive myocardial fructose balance during the fructose infusion. One showed a slight negative

balance at the time of both samplings. In 2 dogs (1 and 6) the coronary sinus concentration of fructose was greater than that in the artery 5 minutes after stopping fructose infusion. Negative myocardial balances of fructose were also detected in other animals 15 and 30 minutes following the onset of infusion.

Discussion. It is known that fructose is rapidly removed from the blood stream after its intravenous injection (Weichselbaum, Elman and Lund[26]). This ability is unimpaired or only slightly impaired in diabetics (Miller *et al.*[17,18], Smith, Ettinger and Seligson[23]). The results obtained in this paper confirm these observations. The

TABLE 2.—MYOCARDIAL USAGE (100 GM. LEFT VENTRICLE PER MINUTE)

	Time (min.)	*Coronary Blood Flow (ml./100 gm./min.)*	*Fructose (mg.)*	*Glucose (mg.)*	*Pyruvate (mg.)*	*Lactate (mg.)*	*Ketones (mg.)*
JW	0	55	0	7.04	0.013	3.67	0.47
	21		−5.17	5.83	0.27	3.68	0.17
	32		−2.14	4.01	0.18	4.92	0.20
RD	0	171	0	9.6	.003	9.36	0.26
	33		−3.3	5.0	0.49	18.9	1.01
FE	0	94	0	4.5	0.21	1.19	0.64
	20		5.1	9.4	0.39	8.88	0.45
	29		6.4	4.9	0.39	7.47	0.34
EP	0	57	0	3.2	0.09	1.82	0.58
	19.5		−0.46	4.2	0.41	6.53	0.31
MR	0	60	0	11.3	0.11	2.48	0.29
	20		−0.36	13.3	0.10	7.08	0.16
	30		−1.2	10.9	0.096	7.48	0.078
BW	0	107	0	2.36	.21	1.07	0.42
	22		9.4	0.75	1.27	8.42	0.18
	32		7.9	4.4	1.38	8.83	0.16
				Diabetics			
HA	0	128	0	−3.8	0.20	1.38	2.74
	19		−2.43	8.3	0.18	1.47	1.27
	28		3.58	21.1	0.05	1.19	2.27
LM	0	109	0	17.4	0.34	0.46	5.11
	22		−0.65	20.3	0.003	0.56	1.91
	33		−2.3	17.4	0.13	0.66	2.68

TABLE 3.—ARTERIAL LEVELS AND ARTERIAL-CORONARY SINUS DIFFERENCES OF FRUCTOSE

	During Infusion				*After Infusion*			
	15 min.		*30 min.*		*5 min.*		*30 min.*	
Dog	*Art.*	*Δ*	*Art.*	*Δ*	*Art.*	*Δ*	*Art.*	*Δ*
1	34.2	0.7	55	1.1	15.5	−4.5	5.7	0.4
2	45.2	2.1	65.9	5.1	24.5	−0.7	7.5	1.8
3	28	2.1	33.5	0.6	11.9	0.2	4	2.1
4	39	−0.8	47.8	14.6	20.7	2.6	4	2.7
5	36.4	−0.8	61.3	−0.3	19.7	0.7	6.5	0.5
6	65.5	1.2	91.3	−2.4	54	−4.2	23.7	0.8

failure to demonstrate consistently high arterial-coronary sinus differences of fructose across the normally functioning myocardium was not surprising. Although muscle tissue contains a fructokinase (Slein, Cori and Cori[22]), there is little utilization of fructose in eviscerated animals (Wick, Sherrill and Drury[28]). The isolated rat diaphragm can metabolize fructose (Haft, Mirsky and Perisutti[10], Mackler and Guest[15]). Utilization is accomplished partly by a nonspecific hexokinase and partly by fructokinase (Mackler and Guest[15]). When both fructose and glucose are presented to the rat diaphragm in equal quantities, the muscle uses glucose preferentially, both for glycogen formation and for oxidation to carbon dioxide (Renold and Thorn[21]). In addition, Hers has shown, using C-14 labeled fructose, that little if any muscle glycogen is derived from direct utilization of fructose[12]. Finally, in man almost all the injected fructose can be accounted for without postulating utilization outside of the splanchnic bed (Mendeloff and Weichselbaum[16]).

The observation that in three of the patients (J.W., R.D., and M.R.) and in 2 animals (1 and 6) considerable negative myocardial balance of fructose was observed, deserves special comment. This could result from inaccuracies in the analytical technique or from the absence of a steady state due to changes in arterial concentration of fructose following and during the infusion. Analytical errors can be excluded, since the recoveries of fructose exceeded 93%. Since changes in plasma fructose levels were part of the experimental design, an effort was made to maintain constant concentrations of this carbohydrate only during infusion. Assuming no uptake of fructose by the heart muscle, a fall in arterial concentration of this carbohydrate should, because of delay through the coronary vascular bed, result in negative myocardial balance of the carbohydrate; however, since the coronary circulation time is less than 2 seconds, this factor appears to be negligible. It is more likely that the negative myocardial balance of fructose results from diffusion of fructose from the heart muscle into the coronary vein blood. Weichselbaum, Margraf and Elman[27] found negative arteriovenous differences across the human extremities following the termination of intravenous fructose infusion. These differences were presumably obtained during falling arterial levels of fructose and were interpreted as back diffusion of fructose from the interstitial fluid, the intracellular fluid, or both. The quantity of fructose found in both muscle and skin biopsies suggested that free fructose was present in both the interstitial and intracellular fluid.

A similar mechanism could possibly explain the data obtained in this series. To confirm this, controlled animal experiments were undertaken in which observations were also carried out during rapidly falling plasma concentrations of fructose. As may be seen from Table 3, the coronary sinus fructose level did exceed the arterial level in 2 of the 6 dogs soon after termination of the infusion. Several other smaller negative A–V differences were found during the infusion (Table 3). The finding suggests that fructose may have diffused out of the heart muscle under these conditions.

The possible mechanism of this back movement of fructose from the intracellular compartment may lie in changes in equilibrium between sugars that can and cannot be metabolized. The heart has at least two compartments available to act as a reservoir for fructose. The first is the interstitial fluid which is in equilibrium with the plasma fructose. During rapidly falling blood levels, the

equilibrium would shift in favor of net movement into the plasma. The second compartment available is the myocardial intracellular fluid. The supposition that this fluid can act as additional fructose reservoir is not out of line with current concepts of sugar transport across cell membranes. Tetanic stimulation of a muscle enhances glucose penetration into the cell by means of unknown mechanisms (Helmreich and Cori[11]). The heart, being continuously active, is thus more permeable to glucose and has a higher intracellular concentration of fermentable sugar than resting skeletal muscle (Helmreich and Cori[11]). Sugars that are very slowly, if at all, metabolized by the cell, may undergo the same type of transport (Park *et al.*[20]). Back movement of sugars from rabbit erythrocytes shows identical rates of transport with sugars entering the cell (Park *et al.*[20]). Presumably this happens in other cells also. The quantitative aspects of this transport system are affected by competition between hexoses. Such competition can both theoretically (Widdas[29]) and actually (Park *et al.*[20]) promote cellular loss of a poorly metabolized sugar against a concentration gradient. Glucose may compete for transport into the cell because this carbohydrate is rapidly utilized in the cell; therefore, there is little competition for back transport into the extracellular fluid. This favors outward movement of a nonmetabolized hexose such as fructose. Final conclusions on the mechanism of this negative fructose balance, however, are not warranted at this time.

On the basis of these considerations, the positive myocardial balance of fructose observed in a series of patients and animals (Fig. 1 and Tables 1 and 3) may be equally explained by net movement out of the intravascular into the interstitial and intracellular compartments. The fact that such positive balance can be observed both during and following intravenous infusion of fructose suggests that factors other than the changes in plasma concentration may be involved in this transfer. It is possible that the degree of cardiac activity may have played a role since Helmreich and Cori[11] could demonstrate a definite influence of electrical stimulation of a muscle on the diffusion of sugar into the cell.

The rise of blood glucose, pyruvate and lactate during the fructose infusion are entirely in keeping with the findings of others (Kaye, Williams and Barbero[14], Miller *et al.*[17,18], Smith, Ettinger and Seligson[23], Weichselbaum, Margraf and Elman[27]). The failure of blood pyruvate to rise as much as one would expect in the presence of rising lactate is probably attributable to the shift in the pyruvate-lactate equilibrium which takes place rapidly in shed blood (Huckabee[13]).

Summary. 1. The arterial and coronary sinus levels of fructose, glucose, lactate, pyruvate and ketones were measured before and during intravenous fructose infusion in 9 nondiabetic and 2 diabetic patients.

2. Positive as well as negative arterial-coronary sinus differences of fructose were found in patients and animals studied. It is possible that this is due to movement of fructose in and out of the heart muscle, as the result of changes in plasma concentration of this carbohydrate. However, other factors such as variations in cardiac activity cannot be excluded.

3. Blood levels of fructose, glucose, lactate and pyruvate rose during the fructose infusion.

4. Myocardial utilization of glucose, pyruvate, lactate and ketone bodies were not noticeably affected by fructose in normals or diabetics.

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SUMMARIO IN INTERLINGUA

Le Metabolismo Myocardial de Fructosa

1. Le nivellos de fructosa, glucosa, lactato, pyruvato, e cetones in le arterias e le sino coronari esseva mesurate in 9 nondiabeticos e 2 diabeticos ante e durante le infusion intravenose de fructosa.

2. Esseva constatate differentias tanto positive como etiam negative inter le valores pro fructosa in le arterias e illos in le sino coronari in le patientes e etiam in animales experimental. Il es possibile que isto esseva le effecto de un diffusion de fructosa in e ex le musculo cardiac, resultante de alterationes del concentration de iste hydrato de carbon in le plasma. Tamen, altere factores—como per exemplo variatic .es del activitate cardiac—non pote esser excludite.

3. Le nivellos sanguinee de fructosa, glucosa, lactato, e pyruvato cresceva durante le infusion de fructosa.

4. Le utilisation myocardial de glucosa, pyruvato, lactato, e cetones non esseva afficite notabilemente per le infusion de fructosa. Isto valeva pro le nondiabeticos e etiam pro le diabeticos.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

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RECENT ADVANCES IN NASAL PHYSIOLOGY

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RECENT studies of the physiology of the nose have cast a beam of light on a field of investigation that has sometimes been characterized by apathy on the part of otolaryngologists. The purpose of this review is to call attention to a number of studies that have sought to revive interest in a specialized area.

The proper preparation of inspired air for acceptable use by the lungs constitutes one of the more important functions of the nasal cavity. During the brief passage through the nasal cavity, inspired air is rapidly subjected to a threefold process of cleansing, moistening, and temperature adjustment. According to Cramer[4], the nasal mucous membrane is primarily concerned with body heat regulation and only secondarily as an air conditioner. Under ordinary conditions a laryngectomized patient can handle inspired air as efficiently as a person having normal nasal anatomical and physiological structures. Cole[3] points out that most of the conditioning occurs before the trachea is reached; however, when the thermal demands are great, humidification extends more distally into the respiratory tract. During mouth-breathing, less humidification is attained at the level of the pharynx than is the case with normal nasal respiration. In the trachea, there is little difference in the degree of humidification between the two.

Expiration contributes greatly to humidification; both heat and water are given up to the mucous membrane, with between a third and a half of the total being conserved. Thus, during expiration there is a reversal of the heat and water exchanges. When the body is heated or cooled, there ensues a rise or fall in the temperature of the pharyngeal inspiratory air and of the

expiratory air at the anterior nares, but this thermal change is not encountered during mouth-breathing. Cole asserts that the upper respiratory mucous membrane in man has a thermo-regulating function similar to that of the skin, the maxillary turbinate being a thermo-regulatory organ that produces thermal changes by controlling the condition of the expiratory air. Ingelstedt and Ivstam[7] found that the humidifying capacity of the human nose is considerable. They placed thermopiles in the nares and connected these to a mirror galvanometer. Evaporation of moisture occurred as humidified air passed over the thermopiles, with a subsequent lowering of the temperature. The relative and absolute humidity was calculated from the difference in temperature between the inhaled and exhaled air. The experiments demonstrated that the nasal mucous membrane has a large reserve capacity for humidifying inspired air.

In order to determine how the various sources of fluid derived from the atmosphere or from tissues of the body by transudation or secretion are regulated so as to maintain a layer of moisture on the mucous membranes of the nose and respiratory tract, Negus[13a,b] studied 2 physical processes, namely transudation of fluid by hydrostatic pressure and active transference by osmosis. The provision of a layer of moisture in the nose and respiratory tract is essential for the functions of olfaction, respiratory exchanges and ciliary action; for the supply of fluid, evidence is advanced in favor of transudation through the epithelium, under the influence of hydrostatic pressure, as being the main bodily source of supply. Secretion from goblet cells and multicellular glands appears to play a minor role in humidification, but water vapor in inspired air is an important but variable factor. Osmosis takes place when water vapor condenses during expiration on areas of the trachea and nose at a temperature below that of the lower air passages, and the moisture thus deposited is practically distilled water. Alterations in the calcium content, together with sympathetic imbalance, result in abnormal permeability and excessive transudation or osmosis, as in allergic states.

According to Scott[15], the nasal mucous membrane of certain animals has the important function of regulating body temperature. In man, the area of the nasal mucous membrane is greatly reduced because the skin has become more efficient as a regulator of heat loss than is the case of animals. Nevertheless, there is a functional correlation between the nasal mucous membrane and skin. In a warm atmosphere the blood vessels of both dilate, and in a cold one they contract. This is controlled by the heat-regulating center in the hypothalamus through the autonomic nervous system and also by certain ductless glands. In an investigation by Fabricant[5a], the topical temperature of clinically normal nasal and pharyngeal mucous membranes was determined in 35 adults (18 men and 17 women). In the 18 men studied, the topical temperature of nasal mucous membranes was found to range from 87.0 to 93.5° F., while the topical temperature of pharyngeal mucous membranes was found to range from 90.5 to 96.0° F. In the 17 women studied, the topical temperature of nasal mucous membranes was found to range from 85.5 to 94.5° F., while the topical temperature of pharyngeal mucous membranes was found to range from 90.0 to 95.5° F. In both men and women, the topical temperature of clinically normal pharyngeal mucous membranes was higher than the topical temperature of clinically normal nasal mucous membranes. Fabricant[5b] points

out that alcoholic beverages have been utilized for generations to abort the common cold, especially after chilling by exposure to inclement weather. Chilling the body surfaces produces a fall in the topical temperature of the nasal mucous membrane, a pronounced reflex vasoconstriction, ischemia, and a diminution of the blood supply. These phenomena occur during the prodromal stages of the common cold. Vascular spasm, ischemia, and anoxemia injure the nasal defenses and pave the way for acute infection. It was found that a measured quantity of an alcoholic beverage produced a rise in the topical temperature of the nasal mucous membranes of 12 adults, 2 of whom were in the prodromal stages of the common cold. The ability to produce a rise in nasal temperature indicates the physiological usefulness of an alcoholic beverage during the prodromal stages of the common cold.

Several studies by Stoksted[16a,b,c] are of interest. The permeability of the nasal passages can be determined with accuracy if the velocity and duration of air-flow through the nose, the minute volume and the frequency of respiration are measured, or can be calculated. He employed anterior rhinometry to determine these values in each nasal cavity. Since the apparatus is both complex and expensive, it is unlikely that his method of investigation will find a place in clinical practice. Clinical judgment will continue to be the basis on which impairment of the airway and the need for surgical intervention will be assessed, at least for the forseeable future.

Holmes[6] declares that it has been demonstrated repeatedly that the alterations in nasal function accompanying conflictual settings are frequently of sufficient magnitude to produce troublesome nasal symptoms and pathologic tissue changes. From a study of the histories of patients exhibiting common nasal disorders and from observations on individuals followed at frequent intervals for long periods of time, it has been possible to establish a correlation between a setting of conflict and anxiety productive of nasal hyperfunction and an exacerbation of nasal disease. Moreover, since conflicts evolving from difficulties in interpersonal and social adjustments often remain unsolved for long periods, the accompanying state of anxiety and nasal hyperfunction may become both intense and sustained. In such a setting the nasal tissues become unable to tolerate the additional alterations in nasal function engendered by new noxious threats or assaults on bodily integrity. Thus, the nasal hyperfunction appearing as a part of an individual's personal and total response to a threatening life situation engendering conflict and anxiety may constitute a major etiologic factor in the genesis of nasal dysfunction. When combined with other environmental stimuli capable of producing nasal hyperfunction, it becomes relevant to the genesis of many common acute and chronic disorders of the nasal and paranasal spaces.

For many years olfaction has not received the same amount of attention as the other special senses. Large gaps still remain in our knowledge of olfactory function. In man, the respiratory functions of the nose have become more important than the olfactory ones; nevertheless, smell is by no means vestigial in human beings, and investigators are beginning to direct their attention to some of the unsolved problems associated with olfaction. It has long been known that for a substance to be odorous it must be volatile, soluble, and capable of reaching the olfactory area in sufficient concentration to produce stimulation. In man, saline is essential, for pure water will

not do as the solvent. Lipoid solubility is also essential, and the degree of solubility of the odorant's molecules in saline and the lipoids varies considerably. The rate of diffusion possibly assists in olfactory discrimination, but whether the discrimination is peripheral or central, or both, has not been definitely established.

In an electro-physiological investigation of the problem, Adrian[1a,b] made recordings of action potentials from the olfactory bulb. When air containing an odorant was breathed, the oscillograph showed discharges with each respiration, which increased in magnitude with increasing concentration of the smell. The general distribution of excitation differed with varying odorants, but not with great variety. With water-soluble odorants the threshold was lower in the anterior part of the olfactory bulb, whereas with lipoid-soluble substances it was lower posteriorly. Each large spike on the oscillograph had a special relation to a particular stimulus, the physical and chemical properties determining the time relationships so that a particular smell could be identified from the tracings. It is theorized that olfactory discrimination may depend on differential sensitivity of the receptors leading to each mitral cell. Since one mitral cell deals with impulses received from many olfactory end-organs in the mucous membrane, vast numbers of combinations are possible, as more than one mitral cell may be involved to a greater or lesser degree. According to Adrian, strong olfactory stimuli produce large sinusoidal waves in the surface layers of the olfactory bulbs. This suggests that they result from synchronized maximal discharges from a great number of units. It is now known that this phenomenon occurs either in the peripheral receptors or in the axons; in other words, a strong odorant causes marked excitation in many receptors which discharge in unison. Further evidence is still required concerning the integration of the responses of the receptors and their axons, and how a particular pattern of afferent impulses evokes a particular sensation in the brain is still unknown. Adrian's work has been confirmed, notably by Le Gros Clark[9], employing the histological approach, and by Mozell and Pfaffman[12] who used electro-physiological methods.

Conclusions drawn from the investigations of Ottoson[14] may be summarized thus: the olfactory hairs of the peripheral olfactory receptors are the sensory elements which respond to stimulation; the olfactory receptors are therefore slowly adapting end-organs with specific sensitivity to particular substances or molecular arrangements; and intimate contact between these molecules and the end-organs is essential to produce stimulation.

Another approach to the problem of olfactory discrimination has been advanced by Moncrieff[11] who has proposed the theory that selective adsorption by the olfactory receptors makes possible the recognition of different odorants. A few dissimilar odorants were shown to behave differently toward such adsorbents as activated carbon and silica gel, but those having an odor of the same general type, such as fruity, were adsorbed in much the same manner. Adsorption characteristics were shown to be related to the particular smell rather than to the chemical composition which varied considerably. Lauffer[8] has emphasized the importance of enzymes, maintaining that the odorant is absorbed upon enzymes found on the surface of the sensory cells. Bartalena[2] has also demonstrated that enzymes play some role in olfaction. When hyaluronidase was placed directly into the nasal passages

odorless substances could be detected. Hyaluronidase was found to increase olfactory perception, but a similar result was procured when anti-hyaluronidase was used. The significance of these findings is not presently apparent.

While there is considerable evidence to support the theory of peripheral discrimination, studies on hematogenic olfaction suggest that there is a central mechanism of olfaction as well. It has long been known that olfactory sensations are aroused when specific substances are injected intravenously. Marco, Morera and Giminez[10] recently examined 44 laryngectomized patients' olfaction by both the nasal and blood-stream routes. By the nasal route, 19 were found to have normal threshold values, 20 showed a raised threshold, and 5 were anosmic. In all the patients, examination of the general nasal sensibility by ammonia was normal, implying that no degeneration had taken place in the sensory endings of the fifth cranial nerve. By the hematic route only 50% of the patients asserted they could recognize the essence of lavender which was injected. In normal subjects all were able to do this. Except in cases of anosmia by the nasal route, hematic stimulation bore no relation to the threshold obtained nasally. These authors conclude that direct stimulation of the centers of olfaction takes place, especially as olfactory sensations can be perceived via the blood-stream by persons who are completely anosmic by the nasal route. To summarize the many conflicting views of olfaction: peripheral discrimination is fairly certain, and here may well be a central mechanism which is as yet unproved. How the stimulus produces its specific effect is debatable, but it is probably in the nature of a physio-chemical reaction. Odor perception may involve several processes, some physical and some chemical.

Finally, the function of the nasal sinuses has been a topic of interest for many generations ever since the days of Vesalius who conceived them to be a means of lightening the bones of the skull in order to maintain balance. Some investigators maintain the nasal sinuses are rudimentary structures which in lower animal forms serve as adjunct to the sense of olfaction. This view is supported by the phylogenetic studies of Negus, insofar as the frontal, ethmoidal and sphenoidal sinuses are concerned. Others state that the nasal sinuses are resonators for the production of the voice, and that they exist as a means of protection or that they are insulators to conserve warmth. Although no general agreement has been reached, comparative anatomical studies suggest that a dual origin can be favored, the upper group of sinuses representing rudimentary olfactory extension, while the lower maxillary sinuses result primarily from unequal development of the respective parts. Secondary functions may be acquired later.

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DERMATOLOGY AND SYPHILOLOGY

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OCULO-CUTANEOUS DISEASES AND INTERNAL MEDICINE: A REVIEW OF SOME OF THE LITERATURE

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SIMULTANEOUS involvement of the skin and eye, frequently observed first either by the ophthalmologist or dermatologist, may be of great importance to the internist since the oculo-cutaneous process can be the external expression of internal disease. The purpose of this presentation is to show the relatively close reationship of these two organs as well as to review some of their concomitant pathological involvement especially that which may be indicative of internal diseases.

The eye and skin share in common an exposed position; other organs, though they may present superficial orifices, are not *per se* external structures. Furthermore, the eye and the skin share an even more basic relationship in that both are derived from the ectoderm[174]. In addition to this common origin, there are also mesodermal components (vascular, lymphatic, supportive, and connective tissues) which enter into the formation of both the eye and the skin and which may be involved simultaneously in disorders of these respective organs. The diseases which affect the skin and the eyes may have a variable relationship to each other; that is, they may represent the same process, and part of the same disease may be present in each organ, or the simultaneous involvement may be coincidence. In addition there are diseases in which the primary effect is on the eye, and the site of secondary involvement is the skin. In other processes the skin is the major tissue implicated with the ocular manifestations of

TABLE 1.—SOME DISEASES INVOLVING THE SKIN AND EYES

I. Heredocongenital and developmental anomalies:
   1. Phacomatoses
      a. Tuberous sclerosis (Bourneville)
      b. Neurofibromatosis (Von Recklinghausen)
      c. Nevus flammeus with glaucoma (Sturge-Weber)
      d. Angiomatosis retinae et cerebelli (Von Hippel-Lindau)
   2. Pseudoxanthoma elasticum and angioid streaks of the retina (Grönblad-Strandberg)
   3. Rothmund's syndrome
   4. Werner's syndrome
   5. Nevoxantho-endothelioma (Metabolic?)
   6. Porphyria congenita (Metabolic?)
   7. Ocular manifestations of sickle-cell disease
   8. Pityriasis rubra pilaris (Avitaminosis A?)
   9. Keratosis follicularis spinulosa decalvans (Siemens)
   10. Dermo-chondro-corneal dystrophy
   11. Ataxia-telangiectasia (cerebellar ataxia, oculocutaneous telangiectasia)
   12. Retrolental fibroplasia and hemangioma of the skin
   13. Ophthalmoplegia, steatorrhea, phlebectasis and vascular lipoma
   14. Symmetric lower lid defects associated with abnormalities of the zygomatic processes
   15. Xeroderma pigmentosum
   16. Epidermolysis bullosa
   17. Albinoidism, piebalding and poliosis
   18. Dermoids and teratomas
   19. Various deformities of eyelashes
   20. Onycholysis partialis semilunaris recidivans and zonular cataract
   21. Pachyonychia congenita with dykeratosis of cornea (cataracts, opacities, and partial blindness)
   22. Blepharochalasis, palpebral dermatolysis
   23. Others, including ichthyosis, colobomata

II. Inflammatory Processes:
   A. Specific infections and parasitic agents
      1. Bacterial: Staphylococci (impetigo, folliculitis, furunculosis, carbuncles); Streptococci (erysipelas [Beta-hemolytic streptococci]); Ritter's disease; granuloma pyogenicum; Morax-Axenfeld diplobacillus; diphtheria; anthrax; glanders; chancroid; tuberculosis; leprosy; rhinoscleroma; granuloma inguinale
      2. Viral: vaccinia; varicella; herpes simplex; zoster; Kaposi's varicelliform eruption; verrucae; molluscum contagiosum; cat-scratch disease; lymphogranuloma venereum
      3. Rickettsial: scrub typhus; Rocky Mountain spotted fever; and others
      4. Fungal: Actinomycosis; blastomycosis; coccidioidomycosis; moniliasis; rhinosporidiosis; tinea; favus; torulosis (cryptococcosis)
      5. Parasitic—protozoan: leishmaniasis (Oriental sore); trypanosomiasis; toxoplasmosis; metazoan—nematodes: infestations of Ascaris, Oxyuris, Ancylostoma, Necator, Trichina, Filaria, Loa Loa, Dracunculus, Schistosoma, Wuchereria, Onchocerca, leeches; spirochetal—arthropoda: Lice (Pediculosis capitis and corporis) scabies; Demodex folliculorum; myiasis; bites and stings: ticks, spiders, chiggers, centipedes, caterpillar (hairs)
   B. Nonspecific
      Vogt-Koyanagi and Harada's syndrome; Behçet's syndrome; erythema multiforme; Stevens-Johnson syndrome (ectodermosis erosiva pluriorificialis); Pemphigoid; Reiter's disease; Sjögren's syndrome; Mikulicz's disease; erythema nodosum; lichen planus and psoriasis; dermatitis herpetiformis; rosacea; sarcoidosis
      Allergic—Specific agents: contactants and sensitizers, drugs, pollens, bacterial products; animal and vegetable proteins
      Physical and nonspecific agents (cold, heat, and light hypersensitivity, atopic dermatitis)

III. Traumatic and toxic
Physical—(thermal; cold; radiation, including—ultra-violet, Roentgen-ray, and radium)
Chemical—acids, alkalies, others
Mechanical—traumatic deformities

IV. Metabolic and pigmentary—Intrinsic (hereditary) and extrinsic: ochronosis; bile pigments; silver; gold; iron; copper and others; diabetes; xanthomatoses (lipoidoses); porphyrias

V. Neoplastic—Nevi; pre-canceroses; malignancies

VI. Degenerative—Senile elastoses; xerosis; cornification; hyaline; amyloid and collagen degeneration, fatty and calcareous degeneration, aging and exposure

VII. Collagen diseases—lupus erythematosus; scleroderma; dermatomyositis; polyarteritis nodosa; rheumatoid nodules

VIII. Vitamin deficiencies—Vitamin A; B-group; C (scurvy); D, and others

IX. Psychogenic—(neurodermatitis, factitial, and others)

a subordinate nature. There are still other conditions which may develop in one and then spread to invade the other organ, either by contiguity or by metastases through blood or lymph channels. Finally, there are cutaneous and ophthalmic disorders which occur together, but whose relationship is undetermined or little understood.

The variety of the diseases which present ocular and cutaneous components is indicated by the extensive but incomplete listing in the table. It is obvious that only a small number of these processes can be detailed in this review. Since we cannot cover the full range of the associated oculo-cutaneous diseases, the reader is referred to appropriate sources of pertinent information[3,71,73a,92b,184,204,231a].

Hereditary and Congenital Diseases of the Eye and Skin. PHACOMATOSES. The phacomatoses have been reviewed as far as the neurological and cutaneous relationships are concerned by Beerman[13b] and by Kirby[123] from the ophthalmological standpoint. This term was introduced by Van der Hoeve[236a] in 1923 to designate the two diseases neurofibromatosis and tuberous sclerosis. Subsequently, Van der Hoeve, and others[236a,236b] amplified the term to imply "spots" of congenital origin in various tissues. Thus, the concept was extended and at present includes: (1) Tuberous sclerosis (Bourneville's disease), (2) Neurofibromatosis (von Recklinghausen's disease), (3) Angiomatosis retinae et cerebelli (von Hippel-Lindau disease), and (4) Nevus flammeus with glaucoma (Sturge-Weber syndrome).

Tuberous Sclerosis. Tuberous sclerosis was first recognized as a pathologic entity in 1880 by Bourneville[29]. The association of papulo-nodular facial skin lesions and potato-like appearance of the affected areas of the brain were thought to be coincidental. In 1906, Vogt[239] described the complete triad of tuberous sclerosis: mental deficiency, epilepsy, and adenoma sebaceum to which the name *epiloia* is often applied. Other reports have indicated that abortive and incomplete forms of this disease occur[7,42,186,213,242]. Tumors involving other organs including the eyes, brain, liver, kidneys, and heart and occasionally the gastrointestinal tract[131] have been observed. Variations from the primary triad may appear and any component may exist

alone or any two may occur with absence or incomplete development of the third, in various combinations.

Symptoms associated with tuberous sclerosis usually arise early in life, often in infancy or early childhood[212,243,245]. Retardation of mental development is frequently the first sign of this disease. The associated epilepsy and adenoma sebaceum may vary in the order of appearance and their onset may be separated by months or years. Most patients die before the age of 20 years. Tuberous sclerosis occurs with equal frequency in both sexes. It is apparently more prevalent in European races, although cases have been recorded in other ethnic groups (Negroes and Japanese). While statistics are available for the incidence in institutional populations (0.1 to 0.6%), there are none for the rate of occurrence of this condition in society at large.

There is considerable evidence that there are heredito-familial characteristics in this disease. It has been reported in identical twins[41,82], and in other members of a single family (5 brothers and sisters[236c]; 5 cases in a family with 9 siblings[235]; a father and 3 children[212]). Certain members of a family may have the entire condition of epiloia while other members may have one or two symptoms of the triad. Cockayne[53] pointed out that the disorder is probably an incomplete dominant trait. In a number of patients it is possible that the disease may have developed by spontaneous mutation as the family history is negative in these cases.

The variety of cutaneous changes which may be associated with tuberous sclerosis in addition to adenoma sebaceum include tumors and hyperplasias, hyperkeratoses, pigmentary disturbances, nevi and nail changes. Butterworth and Wilson[41] pointed out the associated congenital malformations involving mesodermal, as well as ectodermal structures: genital agenesis and other genital disturbances, hydrocephalus, microcephalus and other brain changes; hare-lip, cleft palate, tongue, cheek and ear changes; also defects of the bony skeleton, congenital defects of the cardiovascular system and other viscera. Cares[44] noted that typical skin lesions may be absent in up to 50% of cases.

According to Kirby[123], the most significant objective finding is retinal tumor which was first described by Van der Hoeve[236a], and is documented by Duke-Elder[73a]. Ophthalmoscopic examination, reveals flat, oval, gray areas or large nodular tumors which extend into the vitreous. Both types of lesions may be present in the same eye, and one or both eyes may be affected. Nodular tumors may consist of a small mass of nodules resembling a "white mulberry." The flat gray areas are often multiple, are more common than the nodular tumors, and they generally occupy positions further away from the disc. These tumors are essentially gliomatous.

Neurofibromatosis (Von Recklinghausen's Disease). The lesions of the skin in Von Recklinghausen's disease are primarily tumors of nerve sheaths. Other cutaneous findings include patchy areas of light brown pigmentation (café au lait spots), nevi, and variable sessile and pedunculated fibrous tumors. Formes frustes may be represented by a simple café au lait patch of pigmentation, or a cryptic and asymptomatic subcutaneous tumor. In more severe cases there may be also anomalies of bone, eye, and other developmental abnormalities. The disease occurs in both sexes and cutaneous tumors may be found in infancy, but more commonly begin in puberty or in adult life. Trauma, pregnancy, and the menopause tend to intensify the

condition and severe cases may be fatal. The skin and subcutaneous tumors are flesh-colored lesions varying from a few millimeters to more than 10 cm. They may assume somewhat variable shapes, often pendulous on a narrow stalk. Commonly they are located on the trunk, where a few or hundreds of lesions may be found. They are painless, unless a neuroma develops within the tumor or if the tumor is located at a site of pressure. If such tumors degenerate, they may leave an empty flaccid sac of skin. When neurofibromas develop subcutaneously, they may feel like firm nodules or swellings; if the involvement is extensive, a plexiform neuroma may be formed which feels like a bag of worms. When such neuromas occur in dense aggregates, they may cause enlargement of an extremity, or pendulous, grotesque masses of thickened, loose, pigmented skin hanging in folds from the scalp, face, or trunk. This is known as *elephantiasis neuromatosa* and in the scalp forms *cutis verticis gyrata*. Cranial nerves may be involved; most commonly the acoustic portion of the eighth nerve, resulting in deafness. Likewise, tumors may develop in any part of the sympathetic nervous system, including plexuses and viscera served by these nerves. Mental deficiency, impotence, lack of vigor and other substandard traits are part of the systemic involvement typical of severe cases.

The skin of the eyelids may be the seat of a single or plexiform neurofibroma (with resultant elephantiasis of the lid). More important manifestations are observed on the conjunctivae, the iris, the ciliary body, and the choroid. The process may arise from the ciliary nerves or may originate in the perivascular nerve plexus. The entire choroid and ciliary body may be involved asymptomatically or with glaucoma. Orbital neurofibromatosis may displace the globe leading to proptosis and limitation of movement. The bony orbit may show other deformities. Pulsating exophthalmos has been observed, but the pulsation is *not* expansile and there is no bruit. This helps differentiate neurofibromatosis from carotid-cavernous fistula. Buphthalmos (congenital glaucoma), present at birth, is usually associated with neurofibromatous involvement of the skin about the eye. The retinal and optic disc tumors of neurofibromatosis are often found to be like those of tuberous sclerosis, hence the common designation of phacomatosis. Occasionally, the retinal lesions may resemble Von Hippel's disease[123]. Davis[68] found that the primary optic nerve tumors were mainly gliomas, with some endotheliomas. The latter arise from dural or arachnoid sheaths of the nerve, and resemble meningiomas or meningeal fibroblastomas of the brain. A mixture of these features may be found in some of the tumors with astrocytes as the predominant cell type.

In some cases, mixed findings of tuberous sclerosis and neurofibromatosis may occur[51,167,233]. However, Carol and van Heusden[47] felt that there are no transitions nor combinations of these two diseases.

Encephalotrigeminal angiomatosis (Nevus flammeus and glaucoma, or Sturge-Weber syndrome). Encephalotrigeminal angiomatosis although designated by a number of eponyms, is best known as the Sturge-Weber syndrome. This syndrome has been the subject of many studies for a long time[43,70,123,128,129,143,179,203,221,244a,b]. It is a rare, congenital anomaly and consists of a combination of angiomas of the choroid and pia mater, with homolateral hemangiomas of the skin (nevus flammeus or "port wine stain") in the distribution of one or more of the

branches of the trigeminal nerve. Roentgenographic findings in the skull show characteristic calcifications appearing as sinuous, double-contoured lines within the convolutions of the cortex on the affected side[71,98,249a]. Clinical manifestations include convulsive seizures and hemiplegia which is contralateral to the facial angioma; mental retardation, congenital glaucoma (buphthalmos), and visual disturbances[25a,123,184].

In a study of 35 authentic cases Peterman and his associates[179] found the most common clinical feature was a convulsive disorder in 31 (89%) of the patients. Dermal venous angiomas were present in 30, abnormal roentgenographic findings in 22, mental retardation in 19, ocular involvement in 13, and hemiplegia in 11. The most important ocular manifestations of the Sturge-Weber syndrome is glaucoma, which is often on the same side as the facial nevus. That these vascular nevi and glaucoma can occur bilaterally has been indicated by Bock[26]. Brouwer, Van der Hoeve, and Mahoney[33] reported a case in which a large glioma of the retina was associated with this syndrome. A case showing unilateral vascular nevus on the right side of the face, with contralateral hemiparesis, bilateral congenital glaucoma, mental deficiency, and roentgenographic evidence of characteristic calcification outlining the convolutions of the cortex of the right occipital and parietal lobes with associated cortical atrophy, was reported by Bielawski and Tatelman[21].

Hemangioblastoma of the Retina (angiomatosis and arteriovenous communications in the retina; or Von Hippel-Lindau disease). Van der Hoeve[236b] classified this disease among the phacomatoses on the basis of the finding of a retinal lesion (phakoma). Since cutaneous lesions are rarely found in this process, it will not be discussed further than to note two excellent reviews of this subject by Rados[189] and Kirby[123].

PSEUDOXANTHOMA ELASTICUM (GRONBLAD-STRANDBERG SYNDROME). Although pseudoxanthoma elasticum is uncommon, it is an important medical problem. Its cause is unknown, and no effective treatment is available. The cutaneous lesions consist of asymptomatic yellowish papules which usually coalesce into plaques, and are found on the neck, in the axillae, groin, elbows, knees, and occasionally on the mucosae. They usually develop in adult life. The ocular changes consist of "angioid streaks" of the retina, which are reddish bands occurring about the optic disc. On ophthalmoscopic examination they are seen as irregular streaks radiating throughout the retinal field. Angioid streaks have been described as being white, red, gray, and brown; and the color may change in the course of development. They are almost invariably bilateral. Other changes which may be seen in the retina include: hemorrhages, narrowing of the vessels, and degenerative changes ultimately leading to involvement of the macula with a varying degree of impairment of vision.

The elastic tissue of the vascular tree of the entire body may be affected so that the vessel walls are weakened and hemorrhages occur. Histologically, the collagen appears normal, but masses of basophilic elastic tissue are seen in a wide band extending across the mid portion of the corium undergoing degenerative changes such as fragmentation, disintegration, and clumping; and often infiltrated by calcium deposits. Xanthoma cells are *not* seen. According to Lever[138b], it is the degeneration of the elastic fibers of Bruch's membrane of the retina which causes the small defects and breaks which are

manifested clinically as angioid streaks. Prior to Darier's report[67], a number of authors had observed and recorded degeneration of the elastic tissue; but this was considered to be part of the xanthomatous process.

An excellent resume of pseudoxanthoma elasticum is by Lewis and Clayton[142]. It is interesting to note that while angioid streaks of the retina were described as early as 1892, it remained for Grönblad[101] and Strandberg[220] in 1929, to associate them with pseudoxanthoma elasticum in a conjoint syndrome.

Revell and Carey[195] as well as Szymanski and Caro[223] emphasized visceral involvement in this disease. In addition, they called attention to a number of necropsy reports in the literature, in which there was elastic tissue degeneration of internal organs such as the heart, and various arteries, including: coronary, renal, pancreatic, uterine, and mesenteric. Carlborg[45] has produced a classic monograph on the frequency of the circulatory disturbances as measured by oscillometric, pulse-wave velocity, and arterial elasticity studies. Generalized involvement of the vascular system, consisting of: Hypertension, inequality, and other changes of the pulse, intermittent claudication, angina, Roentgen-ray evidence of calcification of peripheral vessels; abnormal bleeding into the gastrointestinal tract, uterus, bladder, and brain; epilepsy and psychic disturbances have been observed. Diabetes mellitus and thyrotoxicosis also appear to have a greater incidence in this disorder. The sex distribution of this syndrome is about equal, and it is considered to be a recessive or irregularly dominant Mendelian trait[148,222]. There is a sharp rise of incidence of cases after the age of 20 years, reaching a maximum peak in the fifth decade. However, Cahill[42] reported 5 cases occurring in one family and that only female members through three generations were affected. There was no history of consanguinity. Sweitzer and Laymon[222], also found that most patients were women (75%).

Individual systemic findings have been reported in other studies: Wolff, Stokes, and Schlesinger[251] noted intermittent claudication present since early childhood in 2 brothers, ages 14 and 25; degeneration of the elastic tissue and calcification in the walls of vessels[103]; uniform miliary opacities in the lung fields demonstrated roentgenographically[251]; gastrointestinal hemorrhage[252]; peripheral vascular disease[140a]; extensive peripheral vascular disease, gangrene of the lower extremities, widespread calcification of the major blood vessels and extensive calcinosis of subcutaneous tissues; Paget's disease associated with angioid streaks of the retina (the first with pseudoxanthoma elasticum[209]).

Loria and co-workers[148] in 1957, reviewed and added a clinical presentation combined with an electron- and light-microscopic study of a typical case. With the electron microscope; there was no suggestion of damage, distortion, or ultrastructural alteration in the collagen. On the other hand, deposition of foreign matter in or on the elastic tissue was evident in many of the sections studied. No other tissues were found to have similar or related involvement. This finding was consistent with the deposition of mineral (calcium) salts. These results substantiated the conclusion of others that the changes present in this condition are only in the elastic tissue. This was also demonstrated under the light microscope.

ROTHMUND'S SYNDROME. Rothmund's syndrome is an hereditary-familial atrophic poikilo-dermatosis with telangiectasia and striae associated with juvenile

cataracts, as well as certain endocrine features. This disease was first described by Rothmund in 1860[200]. Thannhauser[227a] pointed out that, a multiple germ plasm defect is found in Rothmund's syndrome since, besides the ectodermal, the mesodermal layer (venous disturbances such as subcutaneous distensions and visible telangiectases) is also involved in the malformation. Cole and his co-workers[57] published the first 2 cases of Rothmund's syndrome in the American literature 1945, under the erroneous title of "congenital cataracts in sisters with congenital ectodermal dysplasia." In subsequent correspondence by Thannhauser[227b] the differential diagnosis of ectodermal dysplasia and Rothmund's syndrome was made clear, and was then acknowledged by Cole[56]. There are so many variants and formes frustes that frequent difficulty is encountered in putting such cases under the proper heading from the developmental standpoint. It also remains true that most of the involvement found in the disease is mainly of ectodermal type.

Taylor[226] in 1957 compared this syndrome with Thomson's syndrome, which, having been reported in the early Twentieth Century literature, is essentially Rothmund's syndrome.

WERNER'S SYNDROME. Werner's syndrome has much in common with Rothmund's syndrome and may actually be a variant of the same genetic defect. Werner's syndrome is a type of heredito-familial progeria marked by (1) premature physical senility, including premature baldness, grey hair (canities), precocious cataracts, and arteriosclerosis; (2) clinical scleroderma-like changes, including hyperkeratosis of soles, localized calcification of skin and ulcers occurring over pressure points; (3) endocrine disturbances, hypogonadism and diabetes mellitus in both males and females; and (4) a characteristic physical habitus consisting of short stature, gracile-build, a beak-nose, "bird-faces," and other features of "senescent-juvenilism" which suggest a retarded development.

While Rothmund's syndrome usually begins in the first year of life, the profound changes of Werner's syndrome are not usually evident until the second decade. Also, the changes in body growth, sexual development, osteoporosis, blue sclerae, arteriosclerosis and tight skin with ulceration are not usually manifested in Rothmund's syndrome[184].

Oppenheimer and Kugel[172a] in 1934 reported the first two examples of Werner's syndrome in the American literature. In 1941, they[172b] reported the first necropsy in a case of Werner's syndrome on one of the patients recorded in their previous paper and added observations on an additional case. All cases showed juvenile type of cataracts, and a pluriglandular disturbance was observed, including parathyroid glands, the gonads and thyroid. Recently, additional reports have appeared[178,215].

NEVOXANTHO-ENDOTHELIOMA. Nevoxantho-endothelioma is an uncommon disorder consisting of yellowish tumors appearing on the skin, which often are present at birth, or may have their onset somewhat later, but rarely beyond early childhood. These occur as discrete or grouped firm papules or nodules; they are small and almost never exceed 1 cm. in size. Accurate recognition and diagnosis are important, as the histopathologic picture may be mistaken for sarcoma, but the disease is self-limited and undergoes spontaneous involution, generally complete by the age of puberty.

Senear and Caro[207] as well as Laymon and Schoch[135] consider the lesions to be of the juvenile xanthoma group. Others believe that this process rep-

resents a monosymptomatic form of the Hand-Schüller-Christian syndrome in infants, usually involving only the skin, and of good prognosis. Helwig and Hackney[107] considered the best designation for it to be juvenile xanthogranuloma.

Although Nomland[168] considered nevoxanthoendothelioma as a benign xanthomatous disease of infants and children, a number of cases with visceral involvement (especially the eye, spleen, liver, and lung) have been reported[23,119,133,135,151,153,166,227c]. Newell's[166] 2 patients, aged 10 months and 2 months, both showed a histiocytic infiltration of the eye of the nevoxanthoendothelioma type. In the older infant there were typical cutaneous lesions and secondary glaucoma. Malkinson[151] also reported that the anterior chamber of the eye may be affected with characteristic changes of hemorrhage, histiocytic infiltration of the iris, sclera and conjunctiva.

SICKLE-CELL DISEASE. The ocular manifestations of 5 patients with sickle-cell disease have been described recently by Goodman, Von Sallmann, and Holland[95]. Predominantly, the lesions were vascular in nature, involving the retina, optic disc, and conjunctiva. The fundus changes included retinitis proliferans, aneurysmal vascular dilatations, arborizing vascular networks, focal constriction, sheathing, and obstruction of arterioles and venules, development of chalk-white vessels due to altered intravascular contents, preretinal hemorrhages (simulating retinal tears), and vitreous retinal hemorrhages. Vascular changes were also noted on the optic disc and bulbar conjunctiva. Histologically, some of the following findings were noted: Retinal gliosis, retinal and vitreous hemorrhage, preretinal fibrosis, extensive new vessel formation, obliterated vessels, perivenous lymphocytic cuffing, and sickled-cells intravascularly. These authors discussed their patients in relation to previous reports of sickle-cell retinopathy, along with a consideration of the pathophysiology of sickle-cell disease in other organs and the correlation of ocular pathologic changes with the different genotypic forms of sickle-cell disease.

PITYRIASIS RUBRA PILARIS. Pityriasis rubra pilaris may be limited to certain regions of the body or may be so widespread as to resemble an exfoliative erythroderma. The elementary lesion is an acuminate horny papule involving the follicular orifice. Even in extensive involvement, the individual papules remain discrete and retain their distinctive characteristics and are often recognizable about the hair follicles on the dorsa of the fingers and feel like a nutmeg grater. The face and scalp lesions resemble seborrheic dermatitis. Ectropion may be present.

Under certain circumstances a deficiency of vitamin A provokes a characteristic response in the skin. In recent years, this phrynoderma ("toad-skin") has been associated with other well-established signs of vitamin A deficiency such as xerophthalmia, keratomalacia, and night-blindness.

Brunsting and Sheard[38], reporting on dark adaptation and pityriasis rubra pilaris, have presented several typical cases in which photometric determinations of dark adaptation showed the presence of vitamin A deficiency. However, they feel that it would be presumptuous to assume that the pathogenesis of pityriasis rubra pilaris is to be explained solely on the basis of the deficiency of vitamin A since other factors may play a role in this disease.

KERATOSIS FOLLICULARIS SPINULOSA DECALVANS (SIEMENS). Franceschetti, Jaccottet, and Jadassohn[86] have reported on keratosis follicularis spinulosa decalvans (Siemens) in which

corneal manifestations were noted in an 11-year-old boy, who since the age of 16 months had been suffering from intense photophobia, absence of the temporal part of the eyebrows and roughness of the skin. Slit-lamp examination of the cornea disclosed a dusty superficial affection, as well as a circular peripheral pannus. A younger brother of the patient showed similar but less marked symptomatology. This process is hereditary, transmitted by a sex-linked factor. In persons transmitting the disease it may occasionally manifest itself by an atypical skin lesion without ocular involvement. Histologically, there was nearly complete absence of Bowman's membrane in the cornea and numerous vesicular formations of the epithelium localized mainly in the superficial layers.

DERMO-CUONDRO-CORNEAL DYSTROPHY

Dermo-chondro-corneal dystrophy is a disorder described by Francois[88] in 1949. It consists of symmetrical dystrophic changes in the bones, skin, and eyes. Osseous changes consisted of defective endochondral ossification in only the peripheral portions of the extremities. Dermatologically, the disease was characterized by xanthoma-like excrescences of varying size on the backs of the hands and fingers at the metacarpophalangeal and interphalangeal joints. Similar tumors were present on the dorsal aspects of the elbows and on the nose and ears. Ophthalmologically, the disease manifested itself by bilateral corneal dystrophy with subepithelial opacities, white to brownish and of varying size, some confluent and forming plaques, resulting in severe visual impairment. No other clinical abnormalities were found. Laboratory studies yielded normal findings. Jensen[116] in 1958, reviewed the cases reported by Francois and added another probable one.

ATAXIA-TELANGIECTASIA. Ataxia-telangiectasia is a familial syndrome of progressive cerebellar ataxia, oculo-cutaneous telangiectasia and frequent pulmonary infection. Boder and Sedgwick[27] described 8 cases which they had observed independently. Ataxia-telangiectasia begins in infancy, with progressive cerebellar ataxia, telangiectasia of the bulbar conjunctivae (simulating conjunctivitis), and of the "butterfly area of the face;" frequent sino-pulmonary infection, including bronchiectasis; and peculiarity of eye movements, simulating ophthalmoplegia. Retardation of growth with dwarfing is a frequent feature. While intelligence may be normal in early childhood, it tends to drop below normal range as the ataxia progresses. Pneumoencephalograms give evidence of cerebellar atrophy, and at necropsy there is microscopic evidence of progressive, primary, diffuse, cortical cerebellar degeneration and of enlarged venules in the cerebellar leptomeninges and white matter, without significant changes in the spinal cord.

RETROLENTAL FIBROPLASIA ASSOCIATED WITH HEMANGIOMAS OF THE SKIN. Retrolental fibroplasia occurs mainly in premature infants and consists of capillary proliferation developing on the retina and extending into the vitreous, causing cloudiness and small hemorrhages. The retina may become detached peripherally at first and later completely, leading to complete blindness. Opaque tissue is seen in the cicatricial phase at the periphery of the fundus, eventually covering the entire papillary area and resulting in partial or complete blindness. Reese and Blodi[192] noted that children with retrolental fibroplasia are prone to have hemangiomas of the skin particularly of the eyelids and cheeks. Reese and Payne[193] in a discussion of the persistance and hyperplasia of the primary vitreous pointed out the significant association

of this condition with single or multiple hemangiomas of the skin. They believe that the ocular disease is only a part of a broader clinical picture. An ophthalmologic examination is, therefore, indicated in all premature infants exhibiting hemangiomas of the skin. The basic cause of the fibroplasia is apparently hyperoxia.

OPHTHALMOPLEGIA, STEATORRHEA, PHLEBECTASIA AND VASCULAR LIPOMAS. Bean[9] has reported on a combination of signs and symptoms consisting of ophthalmoplegia with ptosis, anisocoria, diplopia, steatorrhea, phlebectasia, with cold extremities, weakness, and vascular lipomas in a 51-year-old patient who had had the process for approximately 20 years.

SYMMETRIC DEFECTS IN THE LOWER LIDS ASSOCIATED WITH ABNORMALITIES OF THE ZYGOMATIC PROCESSES. Leopold, Mahoney, and Price[137] reported on symmetric defects in the lower lids with loss of eyelashes and Meibomian glands associated with absence of the zygomatic processes in a 3-year-old Negress. Her mother and maternal grandfather displayed identical processes. The abnormalities presented by this family are a hereditary dysostosis with the responsible gene a dominant one.

XERODERMA PIGMENTOSUM. In xeroderma pigmentosum there may be thinning, pigmentation, and ulcerative growths occurring on the lids. The conjunctiva may show marked hyperemia, telangiectasia, and pigmented lesions, which may resemble pingueculae and may run to the edge of the cornea. Especially near the limbus, these may develop into neoplasms. The cornea may become infiltrated and hazy with swollen epithelium. The skin usually becomes involved with numerous malignant tumors and almost always results in relatively early death of the patient. It is an inherited abnormality due to a single recessive gene in which the basic disability is marked sensitivity to sunlight.

EPIDERMOLYSIS BULLOSA. Epidermolysis bullosa, a rare hereditary cutaneous disorder in which the adherence of the epidermis to the dermis is altered, presents itself in two major forms. The first is known as the relatively benign *simple* type, and the destructive and mutilating variety is called the *dystrophic* type. Some patients may not develop their lesions until adult life in which case the process is known as the *acquired* dystrophic type. Generally speaking, ocular lesions are not a prominent feature of any type of this disease. Cohen and Sulzberger[55] report an example of essential shrinkage of the conjunctiva in a case of probable epidermolysis bullosa dystrophica. This is in all likelihood similar to the process known as ocular pemphigus.

ALBINISM, ALBINOIDISM, VITILIGO, AND PIEBALDING. Miscellaneous pigmentary congenital and hereditary diseases. Accounts of them may be found in standard texts of both dermatology and ophthalmology.

Other groups of miscellaneous diseases worthy of mention are:

DERMOIDS AND TERATOMAS. These have been observed also in conjunction with ocular lesions[152].

TRICHIASIS, DISTICHIASIS, TRISTICHIASIS, TETRASTICHIASIS. Other forms of abnormal formations of the eyelashes are well reviewed by Duke-Elder[73a].

ONYCHOLYSIS PARTIALIS SEMILUNARIS RECIDIVANS AND ZONULAR CATARACT. This condition was described by Friedmann[91].

ASSOCIATION OF PACHYONYCHIA CONGENITA WITH DYSKERATOSIS OF CORNEA, CATARACTS, OPACITIES, AND PARTIAL BLINDNESS. Noted by Cockayne[53] and is mentioned also by Pillsbury, Shelley, and Kligman[184].

According to Bluefarb[25b], congenital

cataracts may be found also in cases of poikiloderma vasculare atrophicans.

BLEPHAROCHALASIS—PALPEBRAL DERMATOLYSIS. This process was discussed by Sayoc[201] and Thygeson[231a].

Inflammatory Diseases of the Skin and Eye. Specific Infections and Parasitic Agents. BACTERIAL. Much has been written about the bacterial organisms which may cause infection of both the skin and eye. The lesions which they may produce include: folliculitis, furunculosis, cellulitis, impetigo, ecthyma, carbuncles, erysipelas, the "malignant pustule" of anthrax, diphtheria, chancroid, glanders, rhinoscleroma, Morax-Axenfeld conjunctivitis, hordeola, chalazion, and others, have been extensively studied and reported. For the most part, these organisms and the lesions caused by them will respond to one or another of the wide range of currently available antibiotics. The pyodermas and diphtheria associated with eye and skin infections have been covered by Thygeson[231a]. References to most of the other diseases caused by specific bacterial agents may be found in Duke-Elder's text[73b].

Tuberculosis. Tuberculosis in its various forms, as it affects both the skin and eye, is thoroughly discussed and illustrated by Schönfeld[204]. Givner[92b] and Allende[3] have likewise presented the fundamental findings in tuberculosis of the skin and eye.

Another interesting article on tuberculosis of the eyelid and conjunctiva is that of Sengupta[208].

Leprosy. Leprosy shows numerous ocular manifestations[91a]. These are thoroughly discussed by Duke-Elder[73b]. In addition to involvement of the conjunctiva, cornea, and sclera, diseases of the ocular adnexae are frequently noted, including lepromatous nodules of the eyelids, loss of cilia from the lid margins, as well as alopecia of the outer third of the eyebrows.

Syphilis. In all its stages syphilis may present some findings in the eye, as well as on the skin. The interstitial keratitis of congenital syphilis and rhagades of the mouth are well known. Distinctly less frequent in occurrence are the *primary* lesions (chancres) of the eyelids and conjunctiva, but these too are known and have been described. Less well known is the fact that florid *secondary* eruptions of the skin have their counterpart in the eye, manifested as keratitis, conjunctivitis, and even paresis of the oculomotor nerves. Late lesions (gummata) have been noted on the eyelids, and although seen with far less frequency, are known also to occur on the conjunctiva and sclera.

VIRAL DISEASES OF THE SKIN AND THE EYE. *Vaccinia.* Numerous reports in the literature attest the frequency of vaccinia virus infection of the eyelids. Vaccinial infections of the conjunctiva and cornea are reported less frequently and are usually secondary inoculations from the lids. The eyelid inoculations are usually accidentally self-induced by children who have active anti-smallpox vaccinations[231a]. A few cases have occurred in adults who have inadvertently infected themselves from their children or in the laboratory[177]. In these cases eyelid pustules may be followed by conjunctivitis and keratitis. The corneal infection may occasionally take the form of a disciform keratitis (caused more frequently by other virus, but occasionally by vaccinia). Another review of vaccinia with ocular involvement is that of Atkinson and Scullard[6]. Givner[92b] in his discussion mentions ocular paralysis, optic neuritis, choroiditis, and postvaccinial retinitis. Taylor[225] reported accidental vaccinia of the eyelids and included discussion of the possible modes of infection. The disease is often self-limited, but complications such as symblepharon and corneal ulcer may result.

Eczema Vaccinatum. Eczema vaccinatum may occur in children who are vaccinated while they have an eczema (usually the atopic or infantile form). Mortality rate may be as great as 33%[10].

Kaposi's Varicelliform Eruption. Kaposi's varicelliform eruption is a specific manifestation of the herpes simplex virus. The cutaneous lesions may resemble smallpox and chickenpox. The onset is sudden and new lesions appear for several days. Umbilicated erythematous vesicular elements develop rapidly on the face, head, neck, elbows, and wrists. They become pustular and commonly heal with scarring. Fever often precedes the eruption by 24 hours and may persist for one or 2 weeks. Givner[92b] noted that many patients have atopic dermatitis preceding the onset. He also has seen several cases in which dendritic keratitis has appeared. Brain[30] pointed out that, although Kaposi in 1887 originally described the eruption as varicelliform, it was not until 50 years later that suspicion began to fall on herpes simplex virus, and not until 1941 was this virus actually recovered and identified. It is interesting that Kaposi originally suggested the title of eczema herpetiforme for the disease that has since been called his varicelliform eruption. The severe forms of both diffuse vaccinial eczema (eczema vaccinatum) and Kaposi's varicelliform eruption (due to herpes simplex) may be so similar that they cannot at times be differentiated clinically.

Variola. Variola involves the eyelids in a cutaneous eruption and a catarrhal conjunctivitis. Givner[92b] discussed this and noted that the cornea also may be involved. Duke-Elder[73b] stated that leukomas from hypopyon ulcers of variola were responsible for many cases of blindness before vaccination was popularized.

Herpes Simplex. The lesions of herpes simplex are produced by a virus which is widespread, and probably few human beings escape some form of it during their lifetime[135a]. Many may be quite unaware of its presence, since it adapts itself so well to its host. As has been noted above, it is the agent responsible for Kaposi's so-called varicelliform eruption. Brain[30] reported on the various forms which the process may assume on both skin and mucous membranes. He noted that recurrent herpes may affect the eye, especially the conjunctiva and cornea. In these structures they may appear as small circular opacities and transient vesicles which are seldom apparent to the naked eye. In the cornea a dendritic ulcer may form and occasionally a disciform keratitis. A somewhat less common complication is a relapsing iritis, sometimes of a hemorrhagic type.

Herpes Zoster. (Herpes) zoster is an infectious neuritis caused by a virus which has been isolated, cultured, and identified. While almost any nerve root may be involved, herpes zoster ophthalmicus is the particular form of the eruption which concerns us in this presentation. This occurs when the ophthalmic division of the trigeminal nerve is involved. In this case the eye is affected in about 50% of the patients. Edgerton[75] reviewed this disease and detailed the ocular complications[3,92b, 231b]. He also pointed out the association between herpes zoster and chickenpox, a relationship to which many writers have drawn attention, both on clinical and experimental grounds. Becker[11] has also reviewed the anatomy, etiology, clinical features, and differential diagnosis. He described results of treatment with transfusions of convalescent blood. Keith and Mims[121] reported on the treatment of herpes zoster ophthalmicus with chloramphenicol (chloromycetin). Beard[10] mentions the antihistamines, and corticosteroids as em-

ployed by several authors. Bluefarb[25b] has commented also on herpes zoster ophthalmicus and its management.

Varicella. Varicella, as noted above, has a close relationship to herpes zoster. Some authors believe varicella is the manifestation of the dermatropic form and zoster the lesion of the neurotropic form of the same virus. Givner[92b] has discussed some of the ways in which varicella may affect the cornea. Frandsen[89] has reported extensively on chickenpox in the cornea.

Verruca. The common wart may be found on the eyelids, and particularly on the lid margins. Thygeson[231b] mentioned that conjunctival and corneal papillomas caused by the same virus are believed to occur, but they must be rare indeed compared with lesions of the lids. A superficial keratitis occasionally develops when the verruca involves the lid margin; this can be relieved by removal of the wart.

Molluscum contagiosum. This is primarily a cutaneous disease, but it has important ocular manifestations. According to Thygeson[231b], molluscum contagiosum should be considered a possible cause of every case of unilateral conjunctivitis. A follicular conjunctivitis sometimes complicated by a pannus-forming keratitis may develop; and the disease may be severe enough to simulate trachoma. Removal of the nodule results in prompt cure, indicating that the conjunctival and corneal manifestations are secondary in nature (irritant allergic or toxic) and not true localizations of the virus. In rare instances actual molluscum nodules may form on the conjunctiva or cornea.

Lymphogranuloma venereum. As a cause of chronic conjunctivitis, lymphogranuloma venereum has been reported by Curth, Curth, and Sanders[65]. They also discussed the experimental work which they employed to confirm their diagnosis (namely, inoculation and passage in mice of filtrate from the involved eye of the patient). Scheie, Crandall, and Henele[202] reported 5 cases of keratitis associated with lymphogranuloma venereum. They also tabulated the other ocular lesions which may be associated with lymphogranuloma venereum. Givner[92a] has discussed the background, history, cultural, and morphologic characteristics of this virus as well as its systemic and ophthalmologic expressions.

Cat-Scratch Disease.. Cat-scratch disease (benign lymphoreticulosis) has been reported as one of the causes of Parinaud's syndrome (uniocular granulomatous conjunctivitis with preauricular adenopathy) by Daniels and MacMurray[66], as well as Phillips[181]. Levitt[140] has reviewed the recent and essential literature of the oculoglandular form of cat-scratch disease and reported an additional case.

Other viruses. Various other types of keratitis and conjunctivitis which are considered to be of viral origin have been discussed by Thygeson[231b], including trachoma, inclusion conjunctivitis, epidemic kerato-conjunctivitis, pharyngo-conjunctival fever, New Castle disease conjunctivitis, measles, and mumps keratoconjunctivitis, as well as other forms.

RICKETTSIA. Rickettsia do not play a major role in common findings of both skin and eyes; they are adequately presented by Duke-Elder.

FUNGI. The dermatomycoses as they affect the skin and eyes are well discussed by Thygeson[231a]. In general they are responsible for only a few ocular lesions. Tinea of the scalp may occur in the cilia of the eyelids. Infection of the lids by favus is known to occur, but is extremely rare. The dermatophytids, which are allergic manifestations in persons sensitized by the absorption of fungi or their toxic

products, have occurred on the eyelids, but infrequently as compared with their occurrence elsewhere on the body. No fungi are found in the lesions themselves. Muende[163] has reported on conjunctivitis as a trichophytid manifestation.

The deep mycoses including torulosis, blastomycosis, sporotrichosis, actinomycosis, and cutaneous moniliasis are also adequately discussed by Thygeson[231a]. In addition, Cassady[49] has reported on uveal blastomycosis. Gordon[97] observed a case of ocular sporotrichosis and Arthur[4] recently presented a case of disseminated systemic sporotrichosis with involvement of both skin and eye.

PROTOZOA. Protozoa which affect the skin and the eyes are mainly those of tropical and sub-tropical regions. These include: Oriental sore (leishmaniasis) and trypanosomiasis. These are discussed by Duke-Elder[73b]. An interesting report of a generalized cutaneous eruption associated with chorioretinitis and probably the result of chronic toxoplasmosis was presented by Brennan and his co-workers[31].

METAZOA. The metazoan parasitic infestations of roundworms, flatworms, and leeches are discussed by Duke-Elder[73b]. As to Arthropoda which may infest the skin and ocular adnexae, Thygeson[231a] has reported on pediculosis palpebrarum and trichinosis. Other arthropod affections such as scabies, myiasis and bites and stings due to ticks, spider, chiggers, centipedes, and the allergic irritation of caterpillar hairs are recorded by Duke-Elder[73b].

Nonspecific Inflammatory Dermato-ocular Conditions. Ocular-Mucocutaneous Syndromes. The mucocutaneous syndromes which have ocular involvement include: Behçet's syndrome (and its variants), erythema multiforme exudativum and some of its corollaries, including the pluriorificial type (Stevens-Johnson syndrome), Reiter's syndrome, and other lesser forms. Alice Carleton[46] has aptly stated: "There is a fearsome dermatological jungle in which various diseases with resounding eponymous titles struggle for life. They are the chronic erosive conditions affecting the eyes, mouth, and genitalia. Each specialist is naturally absorbed in his own field, which for him takes precedence over all others, and so a number of syndromes have arisen such as Sutton's (1911) periadenitis mucosa necrotica recurrens, Loblowitz's (1910) ulcus neuroticum oris et vulvae, Lipschütz's (1923) acute vulval ulcer, pustulo-ulcerous balanitis, and others. Behçet (1937, 1940), a Turkish dermatologist, described a triple symptom complex in which all three areas, eyes, mouth, and genitalia, are affected simultaneously or in sequence. Little round or oval ulcers with yellow sloughs succeeded one another in the mouth, vulva, or glans penis, associated with inflammation of the cornea, conjunctivitis, or sclera. The skin has a tendency to develop acneiform pustules or deep-seated lesions of the erythema nodosum type."

"In 1941 Touraine made an extensive study of this whole group. He suggests that the various conditions belong to one single systemic disease which he ascribes to an ultra-virus, and to which he gives the name aphthosis. He thinks that this agent, like the virus of herpes simplex, becomes established in the body and manifests itself clinically when for divers reasons the individual becomes anergic. Touraine divides his apthosis into three groups according to severity and extent." Franceschetti, Valerio, and Babel[87] reviewed the literature on this subject and added 5 cases in which there was recurrent aphthous uveitis with mucocutaneous lesions. Katzenellenbogen[120] reported 3 additional cases of recurrent

aphthous ulceration of oral mucous membrane and genitals associated with recurrent hypopyon iritis. Helen Curth[64a] presented 2 cases of recurrent genito-oral aphthosis and uveitis with hypopyon. Soll[216], who reported 20 cases, found eruptive fever with conjunctivitis, stomatitis, and balanitis in many of them; there was also involvement of the respiratory tract as a counterpart. Additional cases were reported by Thomas[230], Bishav and Mikhail[22], and France and his group[85].

Curth[64b], who had previously reported the first case of this disorder in the United States, presented a general review of Behçet's syndrome along with sections of an enucleated eye showing infiltration of the iris, the ciliary body, choroid, retina, and optic nerve with detachments of the retina, choroid, and posterior portions of the ciliary body, together with hemorrhages and a large exudate. Thibault[229] has reviewed the work of Touraine with regard to ocular manifestations and has reported systemic disturbances affecting the nervous system. Bøe, Dolgaard, and Scott[28] had patients suffering from mucocutaneous ocular syndrome with intestinal involvement, causing death in 4 cases. Evans, Pallis, and Spillane[80] also found involvement of the nervous system in Behçet's syndrome and believe they isolated the virus possibly responsible for this process.

STEVENS-JOHNSON SYNDROME AND VARIANTS. (*Ectodermosis erosiva pluriorificialis*). Ectodermosis erosiva pluriorificialis was reported for the first time under this name in English by Klauder[124] in 1937. This disease is characterized by an acute onset with fever and constitutional symptoms such as headache, chill, malaise, and a vesicular eruption involving notably the hands and feet, accompanied by an inflammation of some or all of the orifices: mouth, nose, conjunctiva, urethra, vagina, and anus. Klauder pointed out the resemblance of this disorder to the human form of foot and mouth disease, and its relation to erythema exudativum multiforme. He felt that ectodermosis erosiva pluriorificialis and Stevens-Johnson syndrome were a part of the broad clinical picture of Hebra's erythema exudativum multiforme, merely displaying some of the vagaries of this disease. Lever[138a] reported 2 cases of severe erythema multiforme (of the ectodermosis erosiva pluriorificialis type) in which a cicatricial conjunctivitis and keratitis were observed in one of his 2 cases. In addition, he pointed out the articular lesions, intestinal lesions, and renal findings which may be associated with erythema multiforme. Lever also noted other diseases which may enter into the differential diagnosis. He, too, felt that other conditions which had been reported under names such as "Ectodermose erosive pluriorificielle," "Dermatostomatitis," and "Eruptive fever with stomatitis and ophthalmia" of Stevens and Johnson were all essentially forms of severe erythema multiforme with predominant involvement of the mucous membranes.

Costello[60] reported on 33 cases, giving details of 17; one with postmortem study. According to Patz[175], the ocular involvement in erythema multiforme may include catarrhal conjunctivitis, followed by secondary bacterial infection, ulceration of the cornea, anterior uveitis; and in cases where the corneal ulcers perforate, a resulting phthisis bulbi.

Other reports have dealt with this process from the standpoint of cause (inclusion bodies)[5], the disease in children[210], the effectiveness of ACTH[237], the clinical features[154], and postmortem findings[171].

REITER'S DISEASE. Reiter's disease is a syndrome characterized by the triad

of urethritis, conjunctivitis and arthritis. According to Montgomery and his colleagues[160], urethritis usually occurs first and is accompanied by a discharge varying from mucopurulent to profuse purulent or bloody secretion. Conjunctivitis most often occurs within 2 weeks and may be mild or severe, with or without a coincident punctate keratitis. The arthritis appears last, usually a few days to 4 weeks following the onset of urethritis and most often involves the finger, knee, foot, and ankle joints. Painless mucous membrane lesions on the penis and the mouth are features considered by some to be specific and of diagnostic value[160a]. Fever is usually present, and this disease must be distinguished from gonococcal arthritis with conjunctivitis and urethritis. Originally described by Reiter in 1916 as "spirochetosis arthritica," it may occur in mild form with remissions occurring within a few weeks, while patients with a severe form may suffer from persistent joint and muscle pain, high fever, rapid weight loss, and marked joint effusions; sometimes accompanied by extensive mucous membrane and skin lesions. By 1949, Peters[180] was able to find 76 cases in the literature for analysis.

The "triple symptom complex" diseases have been compared for differential diagnostic purposes in several studies[64a,64b,144b,198]. There is still considerable controversy about the identity of the various processes in this group. Although there is much evidence for considering them as individual diseases, there is an increasing tendency to classify them all as variants of severe erythema multiforme[197].

SJOGREN'S SYNDROME. Sjögren's syndrome consists of a keratoconjunctivitis sicca, accompanied by salivary gland abnormality and arthritis. The primary complaint in this rare entity is dryness of all mucous membranes and of the skin. There is a general reduction in the secretory capacity of the glands of the body, including the lacrimal, sweat, sebaceous salivary, and upper respiratory mucous glands. Other than dryness and hypohidrosis, skin changes are minimal. It is seen usually in women after the menopause and may be accompanied by polyarthritis and anemia. The cause is not known, but considerable work has been expended on various hypotheses.

Gruber[102] noted that histologically and clinically this disease bears a relationship to sarcoidosis. Others have noted visceral lesions (achalasia of the esophagus[248]). Gordon and Shanbrom[97] also made mention of the systemic manifestations of Sjögren's syndrome with determinations of glandular function, and histologic, bacterial, and viral studies, as well as an extensive consideration of laboratory and radiographic findings in this disease. Kenny and Long[122] suggested that the pathological changes seen in Sjögren's syndrome are related to the degenerative changes occurring in tissues of ectodermal origin in the process of aging.

Morgan[162] in 1954 discussed the probable systemic nature of Mikulicz's disease and its relation to Sjögren's syndrome. He performed a clinical reinvestigation of 18 cases of Mikulicz's disease along with a review of cases of Sjögren's syndrome. In a comparative histologic study of cases of Mikulicz's disease and the microscopic material from the original series of Sjögren, the pathologic changes in the salivary glands were found to be identical. Examination of clinical records showed that a significant number of patients previously considered to have Mikulicz's disease, had other components of Sjögren's syndrome such as keratoconjunctivitis sicca, xerostomia,

and rheumatoid arthritis. Morgan believes that Mikulicz's disease may be a less highly developed variant of a larger symptom complex: Sjögren's syndrome. (Also see Heaton, Sjögren's Syndrome and Systemic Lupus Erythematosus, Brit. Med. J., 1, 466, 1959.)

OCULAR PEMPHIGUS. Ocular pemphigus (benign mucous membrane pemphigoid) is not true pemphigus, and, according to Jablonska and her colleagues[112], it belongs in the group called pemphigoid mucosae. The ocular changes include, initially, symptoms of catarrhal conjunctivitis with a ropy mucoid discharge. Subsequently, there is scarring, thickening, and shrinkage of the conjunctiva, with adhesions running from the bulbar conjunctiva to the eyelids. Eventually, the conjunctival sac is closed completely and the eyeball becomes immobilized (ankyloblepharon). The scar tissue presses upon the lacrimal ducts, causing the conjunctiva and the cornea to become dry. Other mucous membranes may become involved, especially the oral cavity, nasopharynx, larynx, as well as the genital and anal regions. Occasionally, the esophagus and lower parts of the alimentary tract may be involved. Vesicles and bullae may appear on the mucosae; these rupture easily and leave erosions. Shrinking and atrophy of mucous membranes occur. In about half of the cases blisters are seen also on the skin. It may be necessary at times to distinguish it from the bullous type of erythema multiforme, from epidermolysis bullosa and from pemphigus vulgaris. In general, however, it should be noted that pemphigus vulgaris is not marked by shrinkage of the conjunctiva. A number of authorities have assisted in the development of the present concept of this disease[69,126,145,155].

ROSACEA. Rosacea is a chronic hyperemic disease of the skin of the face, often presenting an acneiform component. Ocular involvement in the disease occasionally occurs. Just as there are vascular derangements of the skin, such as telangiectasis, similar manifestations occur in the eye. Patients may complain of pain, burning, and photophobia; blepharitis, conjunctivitis, keratitis, iritis, and episcleritis may occur. Rosacea keratitis may go on to ulceration and subsequent corneal opacities which cause diminution of vision. The ocular component of the rosacea complex has been reviewed by Cawley and Curtis[50], Wise[250], and Beerman[13c].

LICHEN PLANUS. Lichen planus of the eyelids has been reported by Michelson and Laymon[157], as well as by Thygeson[231a].

PSORIASIS. Psoriasis involving the eyelids occurs rarely, and a superficial keratitis has been reported as an occasional complication[231a].

VOGT-KOYANAGI SYNDROME. This rare disease of unknown cause manifests itself as a combination of five clinical findings: uveitis (usually bilateral, nontraumatic, and in which glaucoma may develop); poliosis (premature greying of hair); vitiligo; alopecia (loss of hair); and dysacousia (disturbances in hearing, including tinnitus and loss of hearing). Vogt[239] in 1906 was the first to call attention to several of the findings in this condition. It was Koyanagi[127] in 1929 who added two additional signs, dysacousia and alopecia, to complete the syndrome. Behrman, Levin, and Laval[18] made a pathologic study of the iridic tissue of each eye of the patient, and their initial clinical observation was so early in the course of the disease that the only abnormal finding then was a few cells in the aqueous. Takahashi's[224] experimental findings suggested that a viral agent was responsible. Fine and Gilligan[83] consider this syndrome to be a variant of sympathetic neuropathic ophthalmia,

and is differentiated mainly by the nontraumatic nature of the uveitis. Behrman and his group[18], Givner[92b], and Hague[104] tried in vain to isolate a virus. Lockwood[144b] presented a review of the literature and cited Carrasquillo's[48] exhaustive monograph on the subject. Up to that time some 45 cases had been reported, as well as a number of variants of the basic syndrome. Most cases have been reported from Japan, but a number have been noted in South America, Mexico, the United States, the West Indies, Europe, and China. Five cases have been reported by French[90] in the San Francisco area alone in a recent year. This disease is distributed equally between the sexes and has been found in all strata of society. Besides implicating syphilis and tuberculosis as etiologic agents, other microorganisms have been considered. Anaphylactic sensitization of the uveal pigment, causing the resultant pigmentary changes in the skin and hair, has been postulated. Histologically, the pigment disturbance in the Vogt-Koyanagi syndrome has been shown to be due to a dysfunction of the melanoblasts. Endocrine relationship and the possibility of a vitamin deficiency disease have been entertained also but are presently considered untenable. Commonly, the ocular symptoms appear first with blurring of vision, progressing rapidly to almost complete blindness, followed by slow regression. Precipitates may be found on Descemet's membrane, posterior synechiae, floating opacities, and cataracta complicata. Symptoms of headache and oppressive pain in the eyeballs may accompany the disease. Poliosis may occur a few weeks after the onset of ocular symptoms and may be temporary or permanent. It usually affects the eyebrows, eyelashes, and scalp hair. Vitiligo is usually symmetrical and commonly affects the head, shoulders, and upper extremities. Alopecia, generally of scalp, is patchy and often temporary. Dysacousia accompanying the uveitis is usually bilateral, transitory, and consists of tinnitus, partial deafness, and hyperesthesia to noises. In this disease the general health is unimpaired, but vision rarely returns to normal; finger recognition and perception of light being the usual final result. Treatment does not halt, improve, or change the course of the disease. Only symptomatic and supportive therapy is available. The ophthalmologic problems should be treated as they arise. Bronstein[32] and Soss[218] have reported that steroids may be of some value.

HARADA'S DISEASE. Harada's disease was considered an entity separate from the Vogt-Koyanagi syndrome; since the uveitis associated with it was posterior and was accompanied by retinal detachment, while in the Vogt-Koyanagi syndrome, the uveitis was anterior in situation and no detachment occurred. Reed and co-workers[190] and Yuge[255] feel that this distinction is *not* justified, and that Harada's disease is merely a clinical variant of the Vogt-Koyanagi syndrome. Reed and his co-authors have presented 5 cases which show the great variation that may be encountered in this disease. Perhaps, Vogt-Koyanagi-Harada's disease might be a preferable term.

OCULAR MANIFESTATIONS OF SARCOIDOSIS. This phase of sarcoidosis is fully discussed by Ainslie and James[2] and by James[113]. Details are found also in the papers of Bruntse[39], Reisner[194], and Wegner and Wurm[246]. Jensen[114] presents the manifestations of sarcoidosis of the orbit. Michelson[156] detailed the Heerfordt syndrome (uveoparotitis).

Heerfordt, a Danish ophthalmologist, drew attention to a syndrome characterized by uveitis and enlargement of the parotid glands. It runs a chronic

and usually febrile course, is frequently complicated by cranial nerve palsies, especially of the seventh nerve, and is associated with pleocytosis of the cerebrospinal fluid. Since then a number of investigators[6a,6b,17,35,36,146,147] demonstrated uveoparotid fever as a manifestation of sarcoidosis.

Estimates of the frequency of ocular involvement in sarcoidosis range widely[99]. It is probable that symptomatic lesions are not often overlooked, but less obvious ones are detectable only by slit-lamp examination and will not be recognized unless special interest exists in the subject of ocular sarcoidosis[246]. Often the ocular signs are the first indication of the disease. Such special interest in the Johns Hopkins Hospital has resulted in demonstration of ocular lesions in 60% of patients with the disease. In most series, however, ocular changes are described in only 25 to 30% of the cases. Ainslie and James[2] observed ophthalmologic involvements in 28 of 100 cases. James[113], 1959, later found them in 50 of 200. Kulwin and his group[132] encountered clinical evidence of ocular involvement in 5 of 17 patients. One additional patient showed unilateral keratotic precipitation on ophthalmoscopic examination, which was indicative of previous uveitis. Sarcoidosis may affect the lacrimal glands, conjunctiva, sclerae, the iris, uveal tract, or the retina. Iridocyclitis, the most frequent, is also the most serious ocular disturbance in sarcoidosis. (See James's Tables, page 511.) The frequency of various forms of involvement was as follows in Longcope and Freiman's series: uveitis, 14 cases; iritis, 14 cases; lacrimal glands, 5 cases; eyelids, 5 cases; keratitis, 5 cases; hemorrhagic retinitis, 2 cases; cataract, 2 cases; glaucoma, 2 cases; chorioretinitis, conjunctivitis, episcleritis, and optic atrophy, each, one.

The conjunctiva may be clear or present yellow nodules varying from pinpoint to that of an ordinary chalazion in size. Episcleritis may occur. The cornea may show sclerosing keratitis, keratitis sicca, or diffuse punctate keratitis. The lower part of the cornea is most often affected. The lesions may resolve or cause permanent opacity. The uveal tract may present iridocyclitis as the most common lesion. This iridocyclitis is either acute or chronic. The onset is often insidious with blurring of vision and little or no pain. In these cases no ciliary injection is seen, but cells are present in the aqueous. More often iridocyclitis is severe, with pain, ciliary injection, exudate in the anterior chamber, and nodules on the iris. Posterior synechiae, secondary glaucoma and secondary cataract may ensue. Choroiditis is an infrequent manifestation, occurring as small peripheral lesions or as a disseminated process. Choroidal or retinal masses, retinal or vitreous hemorrhages, and optic neuritis have also been described.

Ocular pain is rarely a symptom. Difficulty in vision, or discomfort giving the sensation of a foreign body, are more commonly the complaints of patients with symptomatic lesions. None of the ocular lesions are specifically characteristic of sarcoidosis. Ophthalmological examination is not a useful means of differentiating sarcoidosis and tuberculosis. Healing without significant residual damage gradually occurs in most patients after months or years; glaucoma and phthisis bulbi with blindness develop in approximately 10%.

The diagnosis of sarcoidosis is a complicated process in some cases. Recently, much hope was held in the results of the exploitation of the Kveim test. Although many investigators[164] have found the Kveim reaction useful

in diagnosis, other observers consider the test unreliable because of the impossibility of maintaining adequate supplies of standardized test materials[111,217]. Additional objections to this test include the difficulties in histologic interpretation and the ever-present danger that the test material has lost specificity[165]. The controversy over the diagnostic value of this test is of little practical concern. Antigen is available for the test only if one prepares and standardizes his own.

TABLE 2.—PRESENTING FEATURES OF OCULAR LESIONS

Type of Ocular Lesion	*Patient (No.)*
Iridocyclitis	30
Subacute (11)	
Chronic (19)	
Conjunctivitis	8
Phlyctenular (4)	
Non-specific (4)	
Keratoconjunctivitis	7
Conjunctival follicles	3
Periphlebitis retinae	1
Cataract	1
Total	50

From James[113]

The remarks by James on the ocular lesions observed in 50 of 200 patients with sarcoidosis summarizes the problem well. The lesions in his cases ". . . included subacute or chronic iridocyclitis, conjunctivitis, keratoconjunctivitis sicca and conjunctival follicles. The differences between subacute and chronic iridocyclitis are striking. This is in part due to corticosteroid therapy, which has probably changed the natural history of sarcoid iridocyclitis. Involvement of other tissues is correlated with ocular disease and the pattern is compared with that observed in patients without eye involvement. Ocular sarcoidosis is commonly accompanied by intrathoracic and cutaneous lesions and by lymphadenopathy. Reduced secretions due to simultaneous lacrimal and salivary gland involvement may superficially resemble Sjögren's syndrome. Compared with those without eye lesions, patients with ocular sarcoidosis belonged to an older age group, females predominated and Mantoux tests were more often negative. The clinical diagnosis should be confirmed, whenever possible, by histological evidence of sarcoid tissue. This was obtained by biopsy of various tissues and also by means of the Kveim test, which was positive in the majority of patients with ocular disease. Blind conjunctival biopsy was of no diag-

TABLE 3.—INVOLVEMENT OF OTHER TISSUES IN OCULAR SARCOIDOSIS

		Other Tissues Involved						
Type of Ocular Lesion	*Patients (No.)*	*Lungs*	*Skin*	*Lymph Nodes*	*Spleen*	*Bone*	*Lacrimal Glands*	*Salivary Glands*
Subacute iridocyclitis	11	10	4	7	2	0	0	2
Chronic iridocyclitis	19	16	8	7	4	5	1	1
Conjunctivitis	8	7	5	2	2	0	0	0
Keratoconjunctivitis	7	4	4	4	0	0	3	3
Conjunctival follicles	3	2	2	3	1	1	0	1
Periphlebitis retinae	1	1	1	1	0	0	0	0
Cataracts	1	1	0	1	1	0	0	0

From James[113]

nostic help. The natural course of sarcoidosis is toward spontaneous healing by fibrosis. In the eye this may cause serious complications, so ocular involvement is an absolute indication for early and energetic corticosteroid therapy."

ALLERGIC DISEASES. Allergic reactions involving the skin are often manifest in the eye and may involve practically all the tissues of the eye. Although they are usually transient, these reactions may at times be quite serious. Leopold and Leopold[136] in 1956 summarized and tabulated the ocular manifestations of allergy. This paper is an excellent working reference to this subject. The material is presented on an anatomical basis: lids, conjunctiva, cornea, uvea, lens, optic nerve, retina, sclera, and orbit.

Theodore[228a,228b] divided eyelid eczemas into three main groups: (1) allergic eczematous dermatitis, due to contact allergy; (2) infectious eczematoid staphylococcal dermatitis, secondary to eyelid infection; and (3) certain generalized dermatoses such as atopic dermatitis, seborrhea, and psoriasis, in which the nonspecific eyelid eczema occurs along with diagnostic lesions elsewhere on the skin. (More will be said concerning atopic dermatitis later in this paper.)

Drug sensitivity is frequently manifested by ocular, as well as cutaneous involvement. Zeller and Deering[257] reported 10 cases of opacification of the corneal epithelium during the course of treatment of arthritis or lupus erythematosus with chloroquine (Aralen) phosphate. The changes appeared to be reversible on cessation of the drug therapy. Hobbs and Calnan[108] reported 22 cases which exhibited similar corneal changes. Most of their cases also showed reversal of the corneal abnormalities after cessation of therapy. However, in one case the visual acuity continued to decrease after therapy was stopped. Allergic edema of the eyelids following the use of diodocaine was reported by Selecha[206].

The atopic diathesis or so-called asthma-hayfever complex has as its cutaneous phase the socalled atopic eczema or atopic dermatitis. This dermatitis is well known to all dermatologists and allergists; and, as part of the examination of these patients, ophthalmoscopic examination is paramount. This is true because a significant complication of atopic dermatitis in the years of adolescence and young adult life is the development of a distinctive form of cataract, an inexplicable complication of the disease. Many reports have appeared in the literature concerning the incidence of this complication, but of special note are those of Cowan and Klauder[61] and Brunsting, Reed, and Bair[37a]. Cowan and Klauder reported an incidence of 8% in 100 patients with atopic eczema. Brunsting *et al.*, reported the results of slit-lamp examinations of the eyes of 1,158 patients with atopic dermatitis observed at the Mayo Clinic from 1940 to 1953. Cataracts of the atopic type were observed in 136 instances, 79 were visible grossly or associated with impaired visual acuity, and 57 were detected by slit-lamp alone. A later report[37b] by these authors gave follow-up examinations on these 57 examinations. Of 36 who replied to a questionnaire, 3 had experienced progression of their cataracts to a stage requiring surgical removal. These were the only ones among the 36 who reported ocular difficulties in which the difficulties could be attributed to progression of the atopic cataracts. Keratoconus, or conical cataract, has also been noted in association with atopic dermatitis. Bereston and Baer[20] reported 2 cases in 1942, and Brunsting and his associates noted 6 persons of the group of 1,158 with

atopic dermatitis to have keratoconus. This process is, therefore, rare. Heredity is thought to be involved in its production.

Metabolic and Pigmentary. LIPID DISEASES. The lipid diseases represent an important internal medical problem. Classified under the general grouping of xanthomatoses, many of the processes have been known for more than a century, but in the past decade great advances have been made in this still poorly understood field. Since a large portion of the manifestations are cutaneous, it is appropriate to indicate that some of the chief contributors to this field are dermatologists: Urbach[232], Montgomery[159], Weidman[247], Polano[185], and Lever[139a,139b]. Thannhauser[227c], an internist, and his group have devoted a tremendous amount of energy to the solution of the problem of the lipidoses and lately, Gofman and his colleagues, in their study of the role of lipoid proteins in the study of atherosclerosis, may have uncovered a fundamental approach to the common denominator operating in the lipidoses of the skin, cardiovascular system, liver, and eye. Recently, studies on the genetics of the xanthomatoses are crystallizing our understanding of the relationship between the hypercholesteremic state and various clinical manifestations in certain families, and suggest an eugenic approach to the eradication of this phenomenon. Along with the improved understanding of the pathogenesis of the lipidoses, new types of disturbances of lipid metabolism are still being described. A number of these new processes are delineated in the papers by Beerman[13a] and by Everett[81]. Many of the lipidoses exhibit ocular manifestations, ranging from peri-ocular yellowish infiltrations, as in xanthelasma, to actual infiltration of the eye by the process similar to that involving the skin, as in the case in certain patients with nevoxanthoendothelioma, cited elsewhere in this presentation.

XANTHELASMA. Xanthelasma, otherwise known as xanthelasma palpebrarum, is the most common type of lipid disease. It appears in the fifth or sixth decade or even earlier and does not have predilection for either sex. The lesions begin as small, yellowish, flat, soft papules, while more advanced lesions are nodules and plaques, involving the eyelids, especially the inner canthi. Larger lesions may obstruct vision. Familial tendency is dependent on frequent association of this type of lipid disease with xanthoma tuberosum and xanthoma disseminatum. It may be the first sign of developing cardiovascular disease and may in about 30 to 40% of cases be associated with various aspects, often severe, of cardiovascular disease, such as hypertension, coronary sclerosis, and angina pectoris. It is also noted among about 10% of lepers and is frequent in diabetics. It is associated with hepatic disease.

Xanthoma tuberosum. Xanthoma tuberosum is the second most frequent type. It is most common in young adults, but may begin at any age. Jews are frequently affected. The eruption consists of yellow to brown papules, nodules, stripes, and plaques, sometimes tumors or pedunculated lesions, especially on the extensor surfaces. The lesions are grouped around the large joints, especially the elbows, knees, hips, and heels. They are rarely flat, except on the palms. The tendon sheaths and synovial membranes may be affected, although in some instances independently. The eyelids may be involved simultaneously. In this process heredity also plays a role. There may be associated cardiovascular disease in about half of the cases. Hepatic processes and myxedema occur in this dis-

ease and the lesions of lupus erythematosus may become xanthomatous. Arcus senilis, as well as many of the other ocular lesions occurring in the diseases mentioned, may be present in patients with tuberous xanthoma. The blood cholesterol is elevated in this form and in the xanthelasma palpebrarum type.

Xanthoma diabeticorum. Xanthoma diabeticorum, more commonly known as xanthoma eruptivum, is not rare. It occurs at any age, less frequently in women, and more commonly in Jews, who are presumably more affected because of the greater incidence of diabetes in this group. The individual lesions resemble those of xanthoma tuberosum, except that they are more numerous and smaller. They consist of yellowish or reddish papules, and confluent plaques. They appear suddenly on the extensor surfaces and on the palms and soles. There may be telangiectasis on the lesions. Itching of variable severity is frequent, and there may be excoriations and secondary pustules. The liver may be enlarged, and the spleen affected, but often subclinically. Because of the severe type of diabetes mellitus associated with this form of cutaneous xanthomatosis, and because of the predilection of diabetes for blood vessels, it is obvious that ocular lesions of diabetes mellitus will occur frequently in these patients.

Nevoxantho-Endothelioma. The ocular lesions of nevoxantho-endothelioma (juvenile xanthogranuloma) have been discussed elsewhere. It is sufficient to point out here that strictly speaking this is not a true xanthoma, nor is it a true nevus. It is more especially important to point out that more and more frequently are ocular manifestations being observed in patients with this disease. This increased reporting and observing of ocular involvement lends more weight to the concept that this disease may, in fact, be a forme fruste of Hand-Schüller-Christian disease.

Miscellaneous Lipidoses. Gaucher's disease may show pingueculae, and Bürger-Grütz xanthomatosis may present jaundice in the normal sites.

Lipoid Proteinosis. Lipoid proteinosis, described originally by Urbach and Wiethe[234], has received considerable attention recently[134,253]. This disease is rather rare, begins in infancy, and has a definite familial tendency (consanguinity). The skin shows nodules, hyperkeratotic and sclerosing types of lesions, particularly on the face, extremities, and mucous membranes, including the larynx, so that hoarseness is a prominent symptom. The tongue may be wood-like in consistency and bound down. The mucosae of the lips and buccal cavity show yellowish-white plaques and firm nodules, and similar changes occur in the epiglottis and vocal cords. Eyelids may be involved. Most papers, in describing cases of this disease, speak of the arrangement of the lesions on the eyelids as giving a beaded appearance. Some authorities believe that lipoid proteinosis (hyalinosis cutis et mucosae) may represent a congenital irritability or fragility of the terminal vessels with transudation of lipoids and proteins into the tissues. This explanation, however, does not give the underlying reasons why the altered blood vessels permit such a selective transudation. Wood, Urbach, and Beerman[253] found that the material deposited in the dermal tissue in lipoid proteinosis was sudanophilic and lipid in character. Histochemical tests suggest that the deposit, at least in their case, might be a galactolipid.

Necrobiosis Lipoidica (Diabeticorum). This disease, now well-known to many fields of medicine, including plastic surgeons, occurs predominantly in women. The lesions are disposed

chiefly on both lower extremities. The primary lesion is a round or oval, smooth, glistening, firm papule embedded in the skin. It enlarges gradually and becomes a plaque. The original color is some shade of yellow with a subsequent admixture of brown, red, or violet. Later, two zones are noted, a central one with buff or russet color and a lighter yellow or yellowish-brown narrow border. In some cases the color varies from bluish-violet at the periphery and a yellow center to a combination of yellow and brown in the center and a wine-colored border. Colors depend on the amount of lipoid and hemosiderin content of the lesions and the degree of stasis of the underlying blood vessels. The surface is smooth, glistening and usually level with the surrounding skin. Finally, the center becomes atrophic and may ulcerate. Because of the frequent association of this process with evidence of diabetes mellitus, it is obvious that all the ocular symptoms of diabetes mellitus may occur in this disease.

PORPHYRIA. The problem of porphyrins, porphyrinuria, and porphyria has been discussed from the chemical standpoint by Zeligman[256] and from other aspects by Beerman and Pastras[16]. The ocular lesions found in a large series[84] of patients with porphyria were described by Barnes and Boshoff[8]. Their patients ranged in age from 8 to 62 years. The ocular lesions included: scarring of the lids and pigmentation following bullous lesions; edema of the eyelids; ectropion; photophobia, and blepharospasm associated with generalized sensitivity to light; loss of elasticity of the skin; laxity of the skin resulting in blepharochalasis; symblepharon; hyaloid thickening of the conjunctiva; pemphigoid occlusion of the fornix; and acute bullous conjunctivitis. In the sclerae, they noted lesions of scleromalacia perforans, often associated with keratomalacic ulcers and corneal scarring. In addition, the cornea may present leukoma adherens, and due to the density of the corneal scarring, blindness may result. The iris and the lens likewise participate in leukoma adherens. Lesions of the fundus were reported also, including patches of exudate and several types of retinal hemorrhages.

PIGMENTARY DISORDERS. The medical importance of cutaneous pigmentation has long been recognized. Beerman and Colburn[14] published a detailed review of this subject. We shall restrict our present remarks to those disorders of cutaneous pigmentation which also show ocular changes as well.

In 1939 Edwards and Duntley[76] demonstrated by spectrophotometric means that five pigments were present in the normal skin. These are carotene, oxyhemoglobin, reduced hemoglobin, melanoid, and melanin. Carotene, precursor to Vitamin A, imparts a yellow color to the skin, being stored in subcutaneous fat and in the stratum corneum. The white-appearance of the conjunctiva is, therefore, understandable as it lacks a well developed stratum corneum. Carotenemia may be differentiated from jaundice by this simple fact, for in jaundice the conjunctiva and sclerae are involved early. In carotenemia these are spared, for they contain neither fat nor keratin. Following an episode of jaundice the sclerae and cornea may be persistently discolored. This is explained on the basis of the bilirubinophilic qualities of these tissues which abound in elastic tissue. Certain drugs and some chemicals used in industry have been found to stain the skin yellow, and at times these are hepatotoxic as well, producing superimposed jaundice. The sclerae may or may not be involved; except that in cases of superimposed jaundice scleral involvement is noted.

Some pigmentary disorders with ocular manifestations are of particular interest to the internist. Gaucher's disease, for example, may present a brownish yellow wedge-shaped thickening or pinguecula of the subconjunctival tissues, usually appearing first on the nasal side of the cornea and then on the temporal side. It has been reported that from 3 to 7% of patients with hyperthyroidism exhibit melanin hyperpigmentation, and Jellinek's sign, a marked hyperpigmentation of the eyelids, is occasionally seen in such patients. Discoloration of the lids and conjunctiva have been reported in ochronosis. Albinism, a congenital loss of pigment, may be partial or complete. Involved in this condition are the skin, hair, and eyes. The Vogt-Koyanagi syndrome (previously discussed) is well known to the dermatologist and ophthalmologist. (Also see Cole, J. G., and Cole, H. G., Incontinentia Pigmenti Associated with Changes in the Posterior Chambers of the Eye, Am. J. Ophthal., **47**, 321, 1959.)

Various metals, whether taken internally, injected intracutaneously, or applied locally, may produce discoloration of the skin. Argyria, due to silver, may frequently involve the conjunctiva[183]. Pigmentation of the lower eyelids has been reported following the administration of gold compounds. Hydrargyria, the brownish pigmentation following the use of topical mercury ointments, is especially prone to occur on the eyelids.

Tumors. The skin around the eyes, especially the lids, offers a fertile field for examination by the internist in search of clues for certain internal diseases. It is true that many of the lesions on the lids of a tumorous nature represent localized disease, and it is necessary to have histologic confirmation of the exact nature of these processes. Mainly to illustrate the variety of these manifestations, we cite the recent study by Welch and Duke[249], of the Wilmer Ophthalmic-Pathology Laboratory of the Johns Hopkins University and Hospital between January 1, 1952, and December 31, 1956, when 617 lid lesions were studied. Three hundred and eight, or 50%, of these lesions were incorrectly diagnosed, illustrating the uncertainty of reliance on clinical impression alone. It is obvious from this study that only a few of the lesions actually represent systemic processes.

Although benign calcifying epithelioma[158,196] is a purely local lesion, it is one which might be construed as representing an expression of calcification of a more general nature. It is, however, completely devoid of systemic effects, but is relatively frequent as is illustrated by the 35 examples of this process reported by Roberts[196].

In his studies of tumors of the eyelids Ronchese[199] points out the value of attention to the changes on the eyelids as an aid to diagnosis and illustrates this by the presentation of a number of benign and malignant processes. Schwab[205] illustrates the variety of eyelid lesions still further by describing the frequent occurrence of syringoma, a benign sweat gland tumor. (*cf* Gaul, L. E., A.M.A. Arch. Ophthal., **53**, 671, 1955.) Howell and Caro[110] have noted lesions of the basal cell nevus in the eyelids. This process is related to multiple cutaneous cancers and associated anomalies of development. Another process of recent interest, not only in ocular circles, but in surgery and internal medicine, and dermatology, is keratoacanthoma of general distribution and including the adnexa. This process has been widely described with respect to the skin surface by many. It is easily confused with carcinoma, both clinically and histopathologically, but in the more extensive forms (multiple keratoacanthoma),

the benign nature is easily discernible[141,182]. With respect to the eye itself Christensen and Fitzpatrick[52] describe the occurrence on the eyelid of an example of this tumor.

Carcinoma of the eyelid[34] itself is not a rare disease. It occurs more commonly in the male and with increasing frequency with age. The course of the disease is variable. Basal cell lesions of the eyelid, as in other sites, invade and destroy adjacent tissue by direct extension, but do not metastasize. In spite of this, serious sequelae may ensue from their extension from the lid to adjacent structures. Prickle cell leions of the eyelid not only spread by direct extension, giving rise to the complication of orbital and sinus invasion, globe destruction and bone involvement characteristic of an untreated basal cell carcinoma, but also tend to metastasize to the orbit and regional lymph nodes. Stetson and Schulz[219] reported 301 cases of this disease. Kaminsky and Segars[118] observed 25 patients with epithelioma of the eyelid in the clinics of dermatology and cancerology of several hospitals in Buenos Aires, Argentina, between 1948 and 1954. Basal cell epithelioma was present in 20 of the cases. They obtained satisfactory functional, esthetic, and therapeutic results from either surgical treatment or radium-puncture in 23 patients, 22 of whom remained in good general condition without recurrence during the follow-up period, which varied from more than one year to over 6 years after the treatment. There was a recurrence in one patient. This is a rather remarkable result in view of the fact that Cogan[54], as well as Haik and his associates[105], echo the well-known irritability of the eye to certain forms of irradiation, Haik's group having observed four examples of cataract following beta-ray radium therapy. On the other hand, Seale[205a] found no damage to the normal adult lens in a series of 19 patients exposed to a dose of 800 to 1,320 gamma radiation. Kaposi's hemorrhagic sarcoma, a disease of widespread visceral involvement may also present ocular lesions[78,169,214].

Among the malignant processes of the superficial tissues of the eye is Bowen's disease of the conjunctiva and cornea. This has the same clinical and histologic features as the similar lesion on the skin surface and is considered by most authorities as an epidermoid carcinoma *in situ*.

Another lesion which has been given considerable attention in the dermatological literature is lymphocytoma cutis[79,106,149,161,242]. In fact, an early discussion of this subject by Epstein recounted the case of a patient whose lesion involved the conjunctiva bulbi. Lymphocytoma cutis, a benign process, is of importance primarily because it may be more or less widespread and may be mistaken for a serious lymphoma. In fact, some patients with this process have had malignant terminations.

PIGMENTARY TUMORS OF THE SKIN AND EYE. The internist and the dermatologist are interested in the pigmentary tumors of skin and eye because many of the lesions may have widespread significance. A number of the problems in this field have been summarized by Beerman, Lane, and Shaffer[15] in this Journal. Among the more interesting processes in this group are the special type of blue nevus called nevus of Ota, and malignant melanoma, particularly the "Malignant Freckle of Hutchinson." The history of the development of our understanding of the nevus of Ota is an example of the importance of knowledge of racial pathology, since this lesion is well-known to the Japanese. In some series of cases as many as 300 examples

have been reported, but in this country in 1949, this lesion was not known as such[173], and the process was called extensive blue patchlike pigmentation, a morphologic variant of blue nevus?, persistent extrasacral Mongolian blue spot?, diffuse mesodermal pigmentation?. Since then, many papers have attested fully to the characteristics of this process; and, in fact, its descriptive name, nevus fusco-caeruleus ophthalmomaxillaris of Ota, fully describes the cutaneous ocular components. Occasionally, this nevus may become malignant[58,72,84,117,188,254].

THE MALIGNANT FRECKLE OF HUTCHINSON. This process has long been known by a variety of names, and in the ophthalmological literature, its features are well-described by Reese[191a,191b] as precancerous and cancerous melanosis of the conjunctiva. Greer[100a,100b] disagrees with Reese's belief that cancerous melanosis is by far the commonest type of malignant melanotic growth of the conjunctiva and that malignant change in a congenital pigmented nevus is rare. Malignant freckle of Hutchinson also points out the importance of age in the determination of prognosis of malignant melanoma which ensues usually in melanotic freckle. Since this freckle occurs in older people, it appears that histologically malignant melanoma is more benign than would be the case if these occurred in younger individuals[125]. The facts regarding the malignant melanoma and its ocular component are fully known to the profession and need not be elaborated at this point, beyond the fact, stating that more continuous series of cases are being reported of metastases to the eye from malignant melanoma of the skin[115]. The problem of some aspects of cutaneous malignancy, particularly metastatic carcinoma to the skin from internal malignancy have been covered by Beerman[13d]. That there is a predilection for some of these metastatic lesions to localize on the skin around the eye, as well as in the eye itself, is illustrated by a recent report by Cowan in which adenocarcinoma of the lid was secondary to adenocarcinoma of the stomach[62].

Collagen Diseases. The diffuse collagen diseases are of great importance to the dermatologist, the ophthalmologist, and the internist. Ordinarily considered under the collagen disease designation are disseminated lupus erythematosus, scleroderma, periarteritis nodosa, dermatomyositis, and rheumatoid arthritis. Some authorities also include Libman-Sachs syndrome, rheumatic fever, Schönlein-Henoch purpura, erythema nodosum, serum sickness, thromboangiitis obliterans, cranial arteritis, ulcerative colitis, and some forms of glomerulonephritis. However, to avoid the controversy surrounding some of the diseases in the latter group, we shall confine our remarks to those five of the first group, generally conceded by most authorities to fall into the category of the diffuse collagen diseases.

Considerable research has been done and much has been written concerning them; but, as yet, the factor which incites these diseases in certain individuals is unknown. Their cutaneous and systemic manifestations are well known, and it is not within the scope of the paper to review them. There are many excellent articles for the especially interested reader[19,24,59,187].

The ocular manifestations of the diffuse collagen diseases are many in number and varied in nature. There are certain of these lesions which are more characteristic of one collagen disease than another; for example, exudative inflammatory lesions are more commonly noted in rheumatoid arthritis, whereas ocular vascular involvement is more frequent in periarteritis

nodosa. Likewise, the "heliotrope eyelids" occur only in dermatomyositis. Yet, when taken together, the ocular manifestations of this group might imply a close relationship between these diseases. While this may be true, it is well to note that at times there is considerable variation as to the type and degree of eye involvement between the various entities. Although toxic retinopathy is common in lupus erythematosus, periarteritis nodosa, and dermatomyositis, rarely, if ever, is there such a pathologic state in scleroderma or rheumatoid arthritis. Conversely cataracts are frequently noted in association with scleroderma (Rothmund's syndrome and Werner's syndrome), but are rarely present in any of the remainder of the group of collagen diseases.

A classic review and discussion of the ocular manifestations of the collagen diseases is that of Hollenhorst and Henderson[109]. Although it was written in 1951, and many papers have appeared since, there have been few additions of note. Only certain elaborations or confirmations of reported findings have appeared in the literature since the appearance of this review. Several of these articles are worthy of note. Goar and Smith[93] reported two cases of rheumatoid arthritis with rheumatoid nodules of the eye, with the histologic picture similar to the nodules about the joints. Aguilera-Maruri and Mirapeix del Cerro[1] reported a case of a 64-year-old woman who had scleroderma since the age of 40 and developed cataracts at the age of 64. This was not considered to be Werner's syndrome (discussed elsewhere in this paper). Macrae and O'Reilly[150] reported 55 cases of systemic lupus erythematosus with eye and ear disorders and 18 cases of periarteritis nodosa with similar disorders. The ophthalmic and neurologic complications (one case) of periarteritis nodosa have been discussed by Sheehan, Harriman, and Bradshaw[211]. Bunim and Black[40] found 28% of their cases of systemic lupus erythematosus to have eye lesions. Bégué, Sidi, Corréard, and Gognies[17] found lupus erythematosus limited exclusively to the eyelids to be rare. Vilanona, Cardenal, and Capdevila[238] have reported 2 cases of chronic lupus erythematosus with localization to the conjunctiva and judge this is not rare. Because of the possibility of ocular changes we suggest that complete ophthalmological examination, including ophthalmoscopy, be performed on all patients suspected of or having one of the collagen diseases, and for repeated examinations during the course of therapy for these processes.

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BOOK REVIEWS AND NOTICES

TUMORS AND TUMOROUS CONDITIONS OF THE BONES AND JOINTS. By HENRY L. JAFFE, M.D., Hospital for Joint Diseases, New York City. Pp. 629; 194 ills. Philadelphia: Lea & Febiger, 1958. Price, $18.50.

OVER the past 30 years, Henry Jaffe has been the author or the co-author of a great number of papers on diseases and tumors of bone. Each paper has eventually become the source for information concerning its subject. In at least six instances, he has supplied the names by which the lesions he has described are now generally known, including fibrous dysplasia, unicameral cyst, benign chondroblastoma, nonosteogenic fibroma, aneurysmal bone cyst and chondromyxoid fibroma. For nearly three decades he has been the arbiter of all controversial aspects of bone pathology and the haven of all pathologists with a problematic diagnosis of a bone lesion. For at least half that long the medical profession has awaited his book, a volume which would be the authoritative work on a very difficult subject.

At long last the book has appeared and it should disappoint no one who consults it. In one volume he has collected and made available what is known of the tumors and tumor-like lesions of bone. The meticulous care with which each subject is handled is admirable. Any deficiency which one may discover in reading it, is not the fault of the book nor the author. It is simply that such deficiencies exist in our knowledge.

There are other good books on bone tumors. There are none so complete, so objective and so free of casual, unproven data. This book will eventually be on the shelves of every thoroughly conscientious physician who must face the problem of bone tumor diagnosis.

E.A.

PENICILLIN. By HAROLD L. HIRSH, M.D., Medical Director, Hebrew Home for Aged; Clinical Instructor of Medicine, Howard University College of Medicine, and LAWRENCE E. PUTNAM, M.D., Assistant Clinical Professor of Medicine, George Washington University School of Medicine, Washington, D.C., Pp. 148; 9 ills. New York: Medical Encyclopedia Inc., 1958. Price, $4.00.

THE reviewer apologizes for the delay in preparing this review. Unfortunately, a bout of influenza interfered with the same; oddly enough, recovery ensued without the use of penicillin. The authors of this monograph have successfully fulfilled their stated purpose: to delineate the usefulness of penicillin and to show the dosage schedules of the various preparations. The chapters devoted to the use of penicillin in those infections in which it is known to be of value are excellent. The authors acknowledge that penicillin administered by mouth is the safest route from the point of view of severe toxic reactions and, at the same time, is equally as effective as parenteral penicillin in a number of penicillin-susceptible infections. In this connection they point out the pharmacological advantages of phenoxymethyl penicillin (Penicillin V) over that of penicillin G. However, according to recent clinical reports, this advantage does not necessarily mean therapeutic superiority. Two pages have been devoted to topical penicillin products; troches, ointments, dental paste, and others, but, in view of the high incidence of sensitization following such routes of administration, this portion of the monograph might well have been given to the condemnation of topical therapy.

In general, this work should be a valuable help to all physicians confronted with the treatment of infections known to be amenable to penicillin therapy. H.F.

STAPHYLOCOCCUS PYOGENES AND ITS RELATION TO DISEASE. By STEPHEN D. ELEK, M.D., D.Sc., PH.D., D.P.H., Professor of Bacteriology, University of London; Consulting Bacteriologist to St. George's Hospital. Pp. 767; 44 ills. Edinburgh and London: E. & S. Livingstone, Ltd. (The Williams & Wilkins Co., Baltimore, exclusive U.S. Agents), 1959. Price, $15.00.

IN an excellent, clearly written text, the author discusses most of the basic knowledge of the coagulase-positive staphylococcus which he prefers to call *Staphylococcus pyogenes*. His good research background qualifies the author to discuss so well in detail the growth requirements, toxins, hemolysins, coagulase and other extracellular metabolites of the organism. He also considers identification by serology and bacteriophage typing, epidemiology, pathogenicity and experimental infections. His evaluation of phage therapy and immunization with toxoid and auto-

genous vaccines points out that little is gained by their use. The current staphylococcal problem and use of antibiotics is discussed but not extensively.

The book is timely because of the present increase in hospital acquired staphylococcal infections, but the thoroughness of the book indicates that it was not written hastily to meet the current need. The bibliography requires 187 pages to list over 4800 references. Most of the papers on clinical experience with staphylococcal infections are excluded from the bibliography. The book has a good subject and author index.

Workers engaged in staphylococcal research, microbiologists, physicians and medical students will profit by reading the book. It is so well done that it should become the standard reference volume for the staphylococcus. Being a major text, the price is proper.

Except for three spelling errors on pages vi and vii and a transposition of plate numbers 2 and 4 in figure 17, the book is remarkably free of errors. K.S.

CHLOROMYCETIN (CHLORAMPHENICOL). By THEODORE E. WOODWARD, M.D., University of Maryland School of Medicine, and CHARLES L. WISSEMAN, JR., M.D., University of Maryland School of Medicine. Pp. 159; 19 ills. New York: Medical Encyclopedia, Inc., 1958. Price, $4.00.

THE early enthusiastic use of chloramphenicol was followed by almost complete abandonment because it was unequivocally implicated in a number of serious, often fatal, blood dyscrasias. Fortunately, this led, for a time, to a more cautious use of chloramphenicol and, for the most part, in selected cases. More recently, however, with the increasing number of stubborn infections, many of which are effectively treated with this drug, the trepidation with which chloramphenicol was formerly used has been somewhat disregarded and the drug is now being used more indiscriminately. Hence, this excellent, authoritative monograph comes at an opportune time. The authors, on the basis of practical experience, have described clearly the therapeutic limitations as well as the toxic manifestations of chloramphenicol. They have stressed the fact that chloramphenicol should be used only after careful consideration of the patient's problem and should be withdrawn at the earliest signs of a toxic reaction. Furthermore, because of the unique antimicrobial properties of chloramphenicol, it should not be employed as a therapeutic panacea for minor, nondescript ailments, but rather should be reserved for specific infections in which other, less toxic agents have proved useless. Certainly, by following this authoritative advice, we may insure this valuable agent's place in therapy. Much has been assembled in this book, which is recommended for use by all practicing physicians, especially those who have forgotten the fate of other effective agents which have lost their usefulness through unwise application and poor planning. H.F.

DIE MEDIKAMENTÖSE BEHANDLUNG DER SCHILDDRÜSENERKRANKUNGEN. By W. GRAB, Pharmacol. Inst., University of Giessen, and K. OBERDISSE, Medical Clinic, Medical Academy Dusseldorf. Pp. 292; 55 ills. Stuttgart: Georg Thieme Verlag, 1959. (Intercontinental Medical Book Corporation, New York, U.S. Agents.) Price, $9.40.

IN the first part of this monograph, Grab presents the pharmacologic basis for drug therapy of thyroid diseases. This section includes a condensed discussion of thyroid physiology and of iodine metabolism. The second section by Oberdisse deals with the clinical aspects under the following chapter headings. I. Laboratory tests; II. Hyperthyroidism; III. Malignant exophthalmos; IV. Thyroiditis; V. Malignant tumors; VI. Goiter; VII. Hyper- and hypometabolism; VIII. Hypothyroidism. The presentation is clear, critical and up-to-date and there is a good bibliography appended to both sections. The "metabolic insufficiency" (without using the term), namely hypometabolism with normal thyroid function, certain symptoms, and good response to triiodothyronine, but not to thyroxine, is presented without any question mark; most American authors have been more critical or doubtful. I was interested in Oberdisse's discussion of the therapeutic use of iodide in hyperthyroidism; I agree entirely with him that this therapy is inadequate (except, again in agreement with the author, preoperatively after adequate treatment with antithyroid drugs). Oberdisse states that in North and West Germany prolonged treatment with iodide is frequently followed by severe exacerbation, even culminating in crisis; this, he states appears to be geographically determined, and not commonly observed in Southern Germany, Austria or the U.S.A. No explanation is attempted. This event he calls "Jodbasedow," evidently a "Jodbasedow" different from that so hotly discussed about two decades ago; then it was stated that in

Austria and Switzerland introduction of iodide as goiter prophylaxis, that is, small amount of iodide caused "Jodbasedow." Such an event, at one time described by European authors, and rarely if ever observed in this country, is discounted by the author (p. 162). A good, up-to-date, readable book. K.P.

THE EFFECT OF ADVANCING AGE UPON THE HUMAN SPINAL CORD. By L. RAYMOND MORRISON with the collaboration of STANLEY COBB and WALTER BAUER. Massachusetts General Hospital, Boston. Pp. 127; 86 ills. Cambridge, Massachusetts: The Commonwealth Fund by Harvard University Press, 1959. Price, $6.00.

THIS is a valuable pictorial atlas of the gross and microscopic changes in the spinal cord resulting from advancing age. The need for this work became apparent following attempted evaluation of the neurological changes occurring in rheumatoid arthritis and in the related collagen diseases. This is a well written, thorough and well documented study of the spinal cord from the second to the ninth decades and represents roughly a fifteen year research project on the part of Dr. Morrison, whose untimely death in 1950, cut short a brilliant career. This collected material is divided into three parts namely histology, atlas and summary and forms the basic control data for study of any abnormalities of the spinal cord. This book is highly recommended. A.P.

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN. By LOUIS WEINSTEIN, PH.D., M.D., Professor of Medicine, Tufts University School of Medicine, Lecturer on Infectious Disease, Harvard Medical School, Chief of the Infectious Disease Service and Senior Physician, Medical Service, New England Center Hospital, Boston, and N. JOEL EHRENKRANZ, M.D., Assistant Professor of Medicine, University of Miami School of Medicine, Chief of the Infectious Diseases Section, Jackson Memorial Hospital, Miami, Florida. Pp. 116; 13 ills. New York: Medical Encyclopedia, Inc., 1958. Price, $4.00.

THE authors, on the basis of many years of laboratory and clinical experience with streptomycin and dihydrostreptomycin, have adequately summarized the present status of these agents, with the exception of their use in tuberculosis. As stated, the need for these agents has been sharply reduced with the introduction of other equally effective and less toxic drugs. The thorny problem of acquired drug resistance to these agents is stressed, as well as superinfections and certain toxic reactions following their use. For the most part, emphasis has been placed on the advantages of combining streptomycin or dihydrostreptomycin with other effective antimicrobial agents. Fortunately, these drugs are used for the most part in hospital practice which should, theoretically, limit their misuse, although streptomycin and dihydrostreptomycin are still often used without sound clinical reason. In this connection, the authors have reminded the surgeon that there is no evidence at hand to show that postoperative morbidity in clean wounds and in routine surgical and obstetrical procedures can be decreased by employing a protective "umbrella" with these, or other, antimicrobial agents.

This monograph should be of particular value as a reference to and source of information about streptomycin and dihydrostreptomycin. H.F.

THE EVALUATION OF DRUG TOXICITY, A SYMPOSIUM. Edited by A. L. WALPOLE AND A. SPINKS, Imperial Chemical Industries, Ltd. Pp. 138; 58 ills. Boston: Little, Brown & Company, 1958. Price, $5.50.

A SYMPOSIUM held in 1957 and containing contributions of the 46 participants from many different disciplines. As indicated by the title, the topic is an important one and is becoming increasingly so with the introduction of many new drugs each year. The problem of determining toxicity of new drugs, both in the laboratory and in clinical medicine, is emphasized. Methods available for determining toxicity and their short-comings are analyzed; the difficulty in predicting clinical efficacy and toxicity from laboratory data is stressed. In addition to more general topics, separate sections are devoted to the special problems of allergic reactions, toxic effects on bone marrow, and liver damage. The questions discussed should be of interest to anyone engaged in the laboratory on clinical evaluation of drugs. R.S.

PHOTOMICROGRAPHY. By ROY M. ALLEN, D.Sc., Fellow and Past President of the New York Microscopical Society. 2nd ed. Pp. 441 ; 235 ills. and 54 plates. Princeton, New Jersey: D. Van Nostrand Company, Inc., 1958. Price $9.00.

THIS is a complete and authoritative text on Photomicrography. It covers the fundamental principles, the equipment, both modern and homemade, the technique and the processing. There is a chapter devoted to the electron microscope and its required techniques. The figures have been carefully selected and are illustrative of the author's written material. In the preface, Dr. Allen points out that photomicrography is no longer a hobby, but is now a science and as such requires the published data and experience of workers in the field. Since audio-visual education is considered to be so important at the undergraduate and graduate level, this book is much needed in both the scientific and commercial fields of teaching. The surgical pathologist should find this text to be extremely valuable, since it furnishes a simplified and comprehensive discussion of photomicrography. A.P.

Metals and Enzyme Activity. Biochemical Society Symposia No. 15. Edited by E. M. CROOK. Pp. 102. New York: Cambridge University Press, 1958. Price, $3.75.

THIS volume contains the proceedings of the 15th in this series of Biochemical Society Symposia which was held at the University of Leeds in July, 1956. Among the topics considered were: The Nature of Metal-Peptide Complexes in Aqueous Solution and the Relationship these have to Proteolytic Activity; The Significance of Heavy Metals in Biological Systems; Univalent Metals and other Loose or Nonspecific Activations; The Role of Metals in Oxidations Catalysed by Xanthine Oxidase and by other Metalloflavoproteins; and Catalytical Active Haemoproteins, with Special Reference to the Cytochromes.

The discussions are comprehensive and basically oriented. Biochemists and other investigators interested in the metallo-enzymes will find much valuable information in this Symposium.

C.Z.

Progress in Cardiovascular Diseases. Edited by CHARLES FRIEDBERG, M.D., Cardiologist and Attending Physician for Cardiology, The Mount Sinai Hospital, New York, Associate Clinical Professor of Medicine, Columbia University. Pp. 108; 23 ills. New York: Grune & Stratton, Inc., 1958. Single-Issue Price, $3.00.

THIS paper-bound volume is Vol. I, No. 1 of a new periodical to be published quarterly. It is considered of sufficient importance to be reviewed as a new book since it may be purchased as a single volume and since it covers the all important, and rapidly developing field of Cardiac Surgery. Subsequent issues this year will cover Progress in Coronary Heart Disease, in Pulmonary Function and Cor Pulmonale and in Diagnostic Methods. The publication is intended to contribute to postgraduate education and to appeal to the general physician as well as to the cardiovascular specialist. The present volume, Progress in Cardiac Surgery, includes contributions by 15 outstanding men. First of all, there is an excellent general survey, including indications for surgery, surgical risk and results by Dr. Friedberg. This is followed by a discussion of the physician's responsibility with respect to surgery in acquired valvular disease by Dr. Paul Wood. This chapter alone should be required reading for all physicians. Dr. Hufnagel then considers the current status of operation for aortic insufficiency. Following this, there are chapters on hypothermia, pump oxygenators, and open heart surgery. The last chapters deal with developments in the correction of certain congenital lesions.

This volume is highly recommended for all physicians who are finding it difficult to keep up with the rapidly progressing field of cardiac surgery. T.D.

Current Concepts of Positive Mental Health. By MARIE JAHODA, Senior Lecturer in Psychology at Brunel College of Technology, England. Pp. 136. New York: Basic Books, Inc., 1958. Price, $2.75.

THIS is the first of a series of monographs to be published by the Joint Commission on Mental Illness and Health as part of a national mental health survey that will culminate in a final report containing findings and recommendations for a national mental health program.

In an interesting, readable book, the author reviews the current concepts of positive mental health. Mental health is viewed in terms of (1) one's attitude toward one's self; others see mental health in terms of (2) the capacity of organism to realize its own potentialities. Mental health is viewed as integration, that is, the relatedness of all processes and attributes in an individual. Perception of reality is a fourth criteria for mental health. Autonomy, self-determination or independence is regarded as the fifth criteria for mental health while mastery of the environment, success and adaptation, is presented as the final criteria. M.B.

Neurological Basis of Behaviour. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.CH., and CECILIA M. O'CONNOR, B.SC. Pp. 400; 109 ills. Boston: Little, Brown and Co., 1958. Price, $9.00.

THIS volume contains the proceedings of an international symposium on the Neurological Basis of Behaviour held in 1957 to commemorate the birth of Sir Charles Sherrington 100 years earlier. It contains a number of reports dealing with various basic investigations in the field. Included are discussions of the behaviour of nerve cells, the neurological basis of responses to stress, the neurophysiological basis of conditioned reflexes and behaviour, brain enzymes and adaptive behaviour, and the relevance of some neurophysiological data to behaviour disorders.

Workers who are concerned with the study of behaviour, normal or abnormal, from the psy-

chologic or psychiatric point of view, will find much of value and interest in these proceedings.

C.Z.

Heredity of the Blood Groups. By A. S. Wiener, M.D., and I. B. Wexler, M.D. Pp. 150; 4 ills. New York: Grune & Stratton, Inc., 1958. Price, $6.00.

During the past few years, there has been rapid progress in the knowledge of blood groups and the application of blood grouping to clinical and legal medicine, as well as to problems in genetics and other areas of biology. The present volume, therefore, comes as a timely and authoritative summary of the contemporary status of human blood groups and their inheritance. It is recommended not only to those directly concerned with blood banks, but to all physicians who may not fully realize the complex immunologic implications which the transfusion of blood holds for their patients.

C.Z.

Dynamic Aspects of Biochemistry. By Ernest Baldwin, B.A., Ph.D., Professor of Biochemistry, University College, University of London. 3rd ed. Pp. 526; 39 ills. New York: Cambridge University Press, 1957. Price, $5.50.

This is the third edition of this widely known book on biochemistry. The author has again given broad coverage to areas of fundamental and general importance, incorporating many discoveries which were made during the 5 years which elapsed since the last edition. New findings referable to transketolation, transaldolation, photosynthesis, oxidative decarboxylation, purine synthesis, and the like have been added, and, of course, the remainder of the text has been brought up-to-date.

Physicians and medical students alike will welcome the latest edition of this authoritative and highly readable volume on biochemistry.

C.Z.

Textbook of Virology. By A. J. Rhodes, M.D., F.R.C.P.(Edin.), F.R.S.C., Director, School of Hygiene, University of Toronto, and C. E. van Rooyen, M.D., D.Sc. (Edin.), M.R.C.P.(Lond.), F.R.C.P.(C). 3rd ed. Pp. 642; 81 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $10.00.

The latest edition of this textbook retains the objective of its predecessors, namely, to present the essential features of virus and rickettsial infections of man. Much new information has been added, including discussions of a number of newly recognized viral diseases.

This volume should be of interest to undergraduate and graduate students of virology, bacteriology, public health, and medicine.

C.Z.

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